

Benzophenones As Inhibitors of Reverse Transcriptase

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Background of the Invention

The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS"), a disease characterized by the destruction of the immune system, particularly of CD4⁺ T-cells, with attendant susceptibility to opportunistic infections, and its precursor AIDS-related complex ("ARC"), a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss. HIV is a retrovirus; the conversion of its RNA to DNA is accomplished through the action of the enzyme reverse transcriptase. Compounds that inhibit the function of reverse transcriptase inhibit replication of HIV in infected cells. Such compounds are useful in the prevention or treatment of HIV infection in humans.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs), in addition to the nucleoside reverse transcriptase inhibitors gained a definitive place in the treatment of HIV-1 infections. The NNRTIs interact with a specific site of HIV-1 reverse transcriptase that is closely associated with, but distinct from, the NRTI binding site. NNRTIs, however, are notorious for rapidly eliciting resistance due to mutations of the amino acids surrounding the NNRTI-binding site (E. De Clercq, *Il Famaco* 54, 26-45, 1999). Failure of long-term efficacy of NNRTIs is often associated with the emergence of drug-resistant virus strains (J. Balzarini, *Biochemical Pharmacology*, Vol 58, 1-27, 1999). Moreover, the mutations that appear in the reverse transcriptase enzyme frequently result in a decreased sensitivity to other reverse transcriptase inhibitors, which results in cross-resistance.

JP 59181246 disclosed certain benzophenones useful as anticancer agents: Certain benzophenone derivatives as inhibitors of HIV-1 reverse transcriptase were disclosed in Wyatt et al. (*J. Med. Chem.* 38:1657-1665, 1995). However, these compounds were primarily active against wild-type HIV-1 reverse transcriptase, rapidly induced resistant virus, and were inactive against a common resistant strain.

We have now discovered that the compounds of the present invention are useful as inhibitors of both wild type and mutant variants of HIV reverse transcriptase.

Brief Description of the Invention

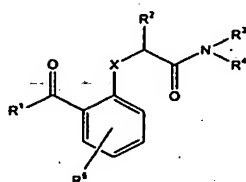
5 A first aspect of the invention features compounds of formula I, IA, IB, IC, ID, II, III, and IV. These compounds are useful in the inhibition of HIV reverse transcriptase, particularly its resistant varieties, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS and/or ARC, either as compounds, pharmaceutically acceptable salts or pharmaceutical composition ingredients. A second
10 aspect of the invention features methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV as monotherapy or in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. A third aspect of the invention features pharmaceutical compositions comprising the above-mentioned compounds and which are suitable for the prevention or treatment of HIV infection. A
15 fourth aspect of the invention features processes for making the above-mentioned compounds.

Detailed Description of the Invention

20 The present invention relates to compounds of formula I, IA, IB, IC, ID, II, III, IV and combinations thereof, or pharmaceutically acceptable salts thereof, in the inhibition of HIV reverse transcriptase and its resistant varieties, the prevention or treatment of infection by HIV and in the treatment of the resulting acquired immune deficiency syndrome (AIDS).

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The present invention features compounds of formula (I)



(I)

wherein:

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X is C, O, or N;

R¹ is C₁₋₈alkyl; C₃₋₆cycloalkyl; C₆₋₁₄aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, -CF₃, C₁₋₈alkyl,

C₁₋₈alkylamino, alkoxy, C₃₋₆cycloalkylC₂₋₆alkenyl, C₆₋₁₄arylC₂₋₆alkenyl, -CN, -NO₂, -NH₂, -SR⁶, -S(O)₂R⁶, -S(O)R⁷, -S(O)₂R⁷, -C(O)R⁷, C₂₋₆alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C₂₋₆alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C₃₋₆cycloalkyl, and heterocycle; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of halogen, C₁₋₈alkyl, -CN, C₆₋₁₄arylC₁₋₈alkyl and heterocycle;

R⁶ is C₁₋₈alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, -CF₃, aryl, and heterocycle;

R⁷ is C₁₋₈alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C₃₋₆cycloalkyl and heterocycle; -NH₂; or heterocycle;

R² is hydrogen, halogen, or C₁₋₈alkyl;

R³ and R⁴ are independently hydrogen; hydroxy; heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC₁₋₈alkyl, halogen, C₁₋₈alkyl, -OR¹¹, -S(O)₂NR⁸R⁹, and -SR¹⁰N(R¹⁰)₂; or C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, -CF₃, C₁₋₈alkyl, hydroxyC₁₋₈alkyl, -CN, -NO₂, C₁₋₈alkylamino, heterocycleC₁₋₈alkyl, -C(O)NH₂, -S(O)R⁷, -S(O)₂R⁷, -C(O)R⁷, -NS(O)₂R⁷, -S(O)₂NR⁸R⁹, -S(O)₂NHR¹¹, -S(O)₂R¹¹, -S(O)₂NR⁷COR¹¹, -S(O)₂NHCOR¹¹, -S(O)₂[COR¹¹]_n wherein n is 1, 2, or 3, -OR¹¹, -OR¹¹OR¹¹, -C(O)R¹¹, -C(O)NR¹¹, -C(O)OR¹¹, -NR¹¹, -NC(O)R¹¹, heterocycleC₂₋₆alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C₁₋₈alkyl, and C(O)OR¹¹, and C₁₋₈alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with -C(O)R¹¹; provided that R³ and R⁴ cannot both be hydrogen or hydroxy;

R⁸ and R⁹ are independently selected from the group consisting of hydrogen, C₃₋₆cycloalkyl, C₁₋₈alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C₆₋₁₄aryl optionally substituted

with alkoxy, C₁₋₈ alkylamino, C₁₋₈alkylheterocycle, heterocycle, heterocycleC₁₋₈alkyl, C₃₋₆cycloalkylC₁₋₈alkyl, and C₃₋₆cycloalkyl;

R¹⁰ is C₁₋₈alkyl;

R¹¹ is C₁₋₈alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, hydroxy, halogen, C₁₋₈alkyl, C₃₋₆cycloalkyl, alkoxy, -S(O)₂NR⁸R⁹, NCONH₂, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, and C₁₋₈alkyl; heterocycle optionally substituted with heterocycleC₁₋₈alkyl; or C₆₋₁₄aryl optionally substituted with alkoxy;

R⁵ is hydrogen, halogen, C₁₋₈alkyl, -NO₂, -NH₂, C₁₋₈alkylamino, CF₃, or alkoxy; or a pharmaceutically acceptable derivative thereof, provided that

(a) when X is N; R¹ is C₆₋₁₄aryl substituted with halogen; R² and R³ are hydrogen; R⁵ is halogen; R⁴ cannot be heterocycle substituted with C₁₋₈alkyl;

(b) when X is C; R² is hydrogen, halogen or C₁₋₈alkyl; R³ is hydrogen; R⁴ is C₆₋₁₄aryl substituted with halogen, hydroxy, or C₁₋₈alkyl; R⁵ is hydrogen, halogen, C₁₋₈alkyl, or alkoxy; then R¹ cannot be C₁₋₈alkyl, C₃₋₆cycloalkyl, or C₆₋₁₄aryl substituted with halogen, C₁₋₈alkyl, alkoxy, or C₆₋₁₄arylC₂₋₆alkenyl; and

(c) when X is C; R² is hydrogen or alkyl, R³ is hydrogen, R⁴ is C₆₋₁₄aryl substituted with halogen, CN, C₁₋₈alkyl, or -NO₂; R⁵ is hydrogen, -NO₂ or NH₂, then R¹ cannot be C₁₀₋₁₄ aryl substituted with alkoxy.

Preferred compounds of formula (I) are those wherein X is O.

More preferred compounds of formula (I) are those wherein X is O; R¹ is C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of halogen, -CF₃, C₁₋₈alkyl, -CN, -SR⁶, -S(O)₂R⁶; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C₁₋₈alkyl, -CN, and C₆₋₁₄arylC₁₋₈alkyl; R⁶ is C₁₋₈alkyl, optionally substituted with halogen; R⁷ is C₁₋₈ alkyl optionally substituted with one or more substituents selected from the group consisting of hydroxy; -NH₂, or heterocycle; R² is hydrogen; R³ is hydrogen or C₁₋₈ alkyl; R⁴ is heterocycle, optionally substituted with one or more substituents selected from the group consisting of

oxo, halogen, C₁₋₈alkyl, -OR¹¹ and -SR¹⁰N(R¹⁰)₂, S(O)₂NR⁸R⁹; or C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, -CF₃, C₁₋₈alkyl, hydroxyC₁₋₈alkyl, -CN, -NO₂, -C(O)NH₂, -S(O)R⁷, -S(O)₂R⁷, -S(O)₂NR⁸R⁹, -OR¹¹, -C(O)NR¹¹, -C(O)OR¹¹, -NR¹¹, -NC(O)R¹¹, and heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C₁₋₈alkyl and heterocycleC₁₋₈alkyl; R⁸ and R⁹ are the same or different and are selected from the group consisting of hydrogen, C₁₋₈alkyl, C₁₋₈alkylheterocycle, heterocycle, and C₃₋₆cycloalkyl; R¹⁰ is C₁₋₈alkyl; R¹¹ is C₁₋₈alkyl, optionally substituted with -SO₂NR⁸R⁹; and R⁵ is halogen or -NO₂; or a pharmaceutically acceptable derivative thereof.

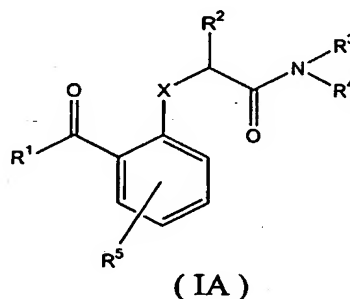
More preferred compounds of formula (I) are those wherein X is O; R¹ is C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of halogen, -CF₃, C₁₋₈alkyl, and -CN; R² and R³ are hydrogen; R⁴ is C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of halogen, C₁₋₈alkyl, -CN, -NO₂, -S(O)R⁷, -S(O)₂R⁷, -NS(O)₂R⁷, wherein R⁷ is -NH₂; and R⁵ is halogen; or a pharmaceutically acceptable derivative thereof.

More preferred compounds of formula (I) are those wherein X is O; R¹ is C₆₋₁₄aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, C₁₋₈alkyl, CF₃, -CN; R² and R³ are hydrogen; R⁴ is C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of C₁₋₈alkyl and S(O)₂NR⁸R⁹, wherein R⁸ and R⁹ are independently selected from the group consisting of hydrogen, C₃₋₆cycloalkyl, C₁₋₈alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C₆₋₁₄aryl optionally substituted with alkoxy, C₁₋₈alkylamino, C₁₋₈alkylheterocycle, heterocycle, heterocycleC₁₋₈alkyl, C₃₋₆cycloalkylC₁₋₈alkyl, and C₃₋₆cycloalkyl.

Other preferred compounds of formula (I) are those wherein R¹ is C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of halogen, -CF₃, C₁₋₈alkyl, and -CN; R² and R³ are hydrogen; R⁴ is C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of halogen, C₁₋₈alkyl, -CN, -NO₂,

-S(O)R⁷, -S(O)₂R⁷, -NS(O)₂R⁷, wherein R⁷ is -NH₂; and R⁵ is halogen; or a pharmaceutically acceptable derivative thereof provided that when X is C; R² and R³ are hydrogen; R⁴ is C₆₋₁₄aryl substituted with halogen, CN, C₁₋₈alkyl, -NO₂; and R⁵ is halogen, then R¹ cannot be C₆₋₁₀aryl substituted with alkoxy.

In another aspect of the present invention compounds of formula (IA) are disclosed:



wherein:

X is C, O, or N;

R¹ is C₆₋₁₄aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, -CF₃, C₁₋₈alkyl, C₁₋₈alkylamino, alkoxy, C₃₋₆cycloalkyl, C₂₋₆alkenyl, C₆₋₁₄arylC₂₋₆alkenyl, -CN, -NO₂, -NH₂, -SR⁶, -S(O)₂R⁶, -S(O)R⁷, -S(O)₂R⁷, -C(O)R⁷, C₂₋₆alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle and C₂₋₆alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C₃₋₆cycloalkyl, and heterocycle;

R⁶ is C₁₋₈alkyl optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, -CF₃, aryl, and heterocycle;

R⁷ is C₁₋₈alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C₃₋₆cycloalkyl and heterocycle; -NH₂; or heterocycle;

R² is hydrogen, halogen, or C₁₋₈alkyl;

R^3 is hydrogen;

R^4 is C_{6-14} aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8} alkyl, hydroxy C_{1-8} alkyl, $-CN$, $-NO_2$, C_{1-8} alkylamino, heterocycle C_{1-8} alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$,
 5 $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-S(O)_2R^{11}$, $-S(O)_2NR^7COR^{11}$, $-S(O)_2NHCOR^{11}$,
 $-S(O)_2[COR^{11}]_n$ wherein n is 1, 2, or 3, $-OR^{11}$, $-OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$,
 $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycle C_{2-6} alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8} alkyl, and $C(O)OR^{11}$, and C_{1-8} alkyl which may be optionally substituted
 10 with one or more substituents selected from the group consisting of $-CN$ and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^8 and R^9 are independently selected from the group consisting of hydrogen, C_3-6 cycloalkyl, C_{1-8} alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14} aryl optionally substituted
 15 with alkoxy, C_{1-8} alkylamino, C_{1-8} alkylheterocycle, heterocycle, heterocycle C_{1-8} alkyl, C_{3-6} cycloalkyl C_{1-8} alkyl, and C_{3-6} cycloalkyl;

R^{11} is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, hydroxy, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, alkoxy, $-S(O)_2NR^8R^9$, $NCONH_2$, and heterocycle optionally substituted with one or more
 20 substituents selected from the group consisting of oxo, hydroxy, and C_{1-8} alkyl; heterocycle optionally substituted with heterocycle C_{1-8} alkyl; or C_{6-14} aryl optionally substituted with alkoxy;

R^5 is hydrogen, halogen, C_{1-8} alkyl, $-NO_2$, $-NH_2$, C_{1-8} alkylamino, CF_3 , or alkoxy; or a pharmaceutically acceptable derivative thereof provided that

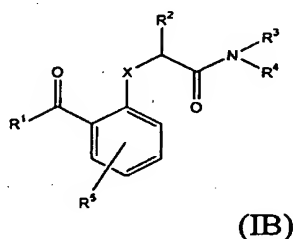
25 a) when X is C ; R^2 is hydrogen, halogen or C_{1-8} alkyl; R^3 is hydrogen; R^4 is C_{6-14} aryl substituted with halogen, hydroxy, or C_{1-8} alkyl; R^5 is hydrogen, halogen, C_{1-8} alkyl, or alkoxy; then R^1 cannot be C_{1-8} alkyl, C_{3-6} cycloalkyl, or C_{6-14} aryl substituted with halogen, C_{1-8} alkyl, or C_{6-14} aryl C_{2-6} alkenyl; and

(b) when X is C ; R^2 is hydrogen or alkyl; R^3 is hydrogen; R^4 is C_{6-14} aryl substituted with halogen, CN , alkyl, or $-NO_2$; R^5 is hydrogen, $-NO_2$, or NH_2 , then R^1
 30 cannot be C_{10-14} aryl substituted with alkoxy.

Preferred compounds of formula (IA) are compounds wherein X is O.

More preferred compounds of formula (IA) are compounds wherein X is O; R¹ is C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of halogen, -CF₃, C₁₋₈alkyl, -CN, C₂₋₆alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle and C₂₋₆alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C₃₋₆cycloalkyl, and heterocycle; R² and R³ are hydrogen; R⁴ is C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of C₁₋₈alkyl, -S(O)₂R⁷, -S(O)₂NR⁸R⁹, -OR¹¹, heterocycleC₂₋₆alkenyl, and heterocycle which may be optionally substituted with oxo; and R⁵ is halogen; or a pharmaceutically acceptable derivative thereof.

In a further aspect of the present invention there is provided compounds of formula (IB):



wherein:

X is C, O, or N;

R¹ is C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of halogen, -CF₃, C₁₋₈alkyl, C₁₋₈alkylamino, alkoxy, C₃₋₆cycloalkylC₂₋₆alkenyl, C₆₋₁₄arylC₂₋₆alkenyl, -CN, -NO₂, -NH₂, -SR⁶, -S(O)₂R⁶, -S(O)R⁷, -S(O)₂R⁷, -C(O)R⁷, C₂₋₆alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C₂₋₆alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C₃₋₆cycloalkyl, and heterocycle;

R⁶ is C₁₋₈alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, -CF₃, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, aryl, C_{3-6} cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

5 R^2 is hydrogen, halogen, or C_{1-8} alkyl;

R^3 is hydrogen;

R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxy C_{1-8} alkyl, halogen, C_{1-8} alkyl, $-OR^{11}$,
10 $-SR^{10}N(R^{10})_2$, and $-S(O)_2NR^8R^9$;

R^8 and R^9 are independently selected from the group consisting of hydrogen, C_3 -
6cycloalkyl, C_{1-8} alkyl optionally substituted with one or more substituents selected
from the group consisting of oxo, heterocycle, CN and C_{6-14} aryl optionally substituted
with alkoxy, C_{1-8} alkylamino, C_{1-8} alkylheterocycle, heterocycle, heterocycle C_{1-8} alkyl,
15 C_{3-6} cycloalkyl C_{1-8} alkyl, and C_{3-6} cycloalkyl;

R^{10} is C_{1-8} alkyl;

R^{11} is C_{1-8} alkyl, optionally substituted with one or more substituents selected from
the group consisting of hydrogen, hydroxy, halogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, alkoxy,
 $-S(O)_2NR^8R^9$, $NCONH_2$, and heterocycle optionally substituted with one or more
20 substituents selected from the group consisting of oxo, hydroxy, and C_{1-8} alkyl;
heterocycle optionally substituted with heterocycle C_{1-8} alkyl; or C_{6-14} aryl optionally
substituted with alkoxy;

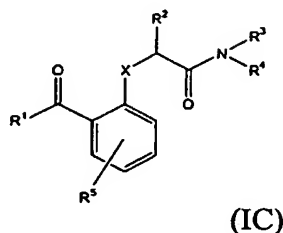
R^5 is hydrogen, halogen, C_{1-8} alkyl, $-NO_2$, $-NH_2$, C_{1-8} alkylamino, CF_3 , or alkoxy;
25 or a pharmaceutically acceptable derivative thereof provided that when X is N; R^1 is C_{6-14} aryl substituted with halogen; R^2 and R^3 are hydrogen; R^5 is halogen; R^4 cannot be
heterocycle substituted with C_{1-8} alkyl.

Preferred compounds of formula (IB) are those wherein X is O.

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More preferred compounds of formula (IB) are those wherein X is O; R^1 is C_{6-14} aryl
substituted with one or more substituents selected from the group consisting of halogen,
 $-CF_3$, and $-CN$; R^2 is hydrogen; R^3 is hydrogen; R^4 is heterocycle; and R^5 is halogen; or a
pharmaceutically acceptable derivative thereof.

In another aspect of the present invention there is provided compounds of formula (IC)



wherein:

10 X is C, O, or N;

R¹ is heterocycle, optionally substituted with one or more substituents selected from the group consisting of C₁₋₈alkyl, halogen, -CN, C₆₋₁₄arylC₁₋₈alkyl and heterocycle;

15 R² is hydrogen, halogen, or C₁₋₈alkyl;

R³ is hydrogen;

R⁴ is C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, -CF₃, C₁₋₈alkyl, hydroxyC₁₋₈alkyl, -CN, -NO₂, C₁₋₈alkylamino, heterocycleC₁₋₈alkyl, -C(O)NH₂, -S(O)R⁷, -S(O)₂R⁷, -C(O)R⁷, -NS(O)₂R⁷, -S(O)₂NR⁸R⁹, -S(O)₂NHR¹¹, -S(O)₂R¹¹, -S(O)₂NR⁷COR¹¹, -S(O)₂NHCOR¹¹, -S(O)₂[COR¹¹]_n wherein n is 1, 2, or 3, -OR¹¹, -OR¹¹OR¹¹, -C(O)R¹¹, -C(O)NR¹¹, -C(O)OR¹¹, -NR¹¹, -NC(O)R¹¹, heterocycleC₂₋₆alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C₁₋₈alkyl, and C(O)OR¹¹, and C₁₋₈alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with -C(O)R¹¹;

R⁷ is C₁₋₈ alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C₃₋₆cycloalkyl and heterocycle; -NH₂; or heterocycle;

R⁸ and R⁹ are independently selected from the group consisting of hydrogen, C₃₋₆cycloalkyl, C₁₋₈alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C₆₋₁₄aryl optionally substituted

with alkoxy, C₁₋₈ alkylamino, C₁₋₈alkylheterocycle, heterocycle, heterocycleC₁₋₈alkyl, C₃₋₆cycloalkylC₁₋₈alkyl, and C₃₋₆cycloalkyl;

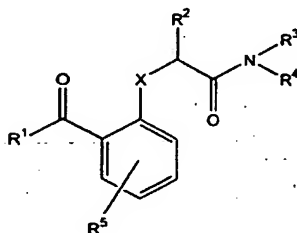
R¹¹ is C₁₋₈alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C₁₋₈alkyl, alkoxy, -S(O)₂NR⁸R⁹, -NR⁸R⁹, and
 5 heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C₁₋₈alkyl;

R⁵ is hydrogen, halogen, C₁₋₈alkyl, -NO₂, -NH₂, C₁₋₈alkylamino, CF₃, or alkoxy;
 or a pharmaceutically acceptable derivative thereof.

10 Preferred compounds of formula (IC) are those wherein X is O.

More preferred compounds of formula (IC) are those wherein X is O; R¹ is heterocycle, optionally substituted with -CN; R² and R³ are hydrogen; R⁴ is C₆₋₁₄aryl substituted with one or more substituents selected from the group consisting of C₁₋₈alkyl,
 15 -S(O)₂NR⁸R⁹, -OR¹¹, and heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo; and R⁵ is halogen; or a pharmaceutically acceptable derivative thereof.

20 The present invention also features compounds of formula (ID):



(ID)

25 wherein:

X is C, O, or N;

30 R¹ is heterocycle, optionally substituted with one or more substituents selected from the group consisting of C₁₋₈alkyl, halogen, -CN, C₆₋₁₄arylC₁₋₈alkyl and heterocycle;

R² is hydrogen, halogen, or C₁₋₈alkyl;

R³ and R⁴ are independently hydrogen; hydroxy; heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC₁₋₈alkyl, halogen, C₁₋₈alkyl, -OR¹¹, -S(O)₂NR⁸R⁹, and -SR¹⁰N(R¹⁰)₂; or R³ and R⁴ together with the nitrogen atom to which they are attached form a heterocycle which may be optionally substituted with C₆₋₁₄aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C₁₋₈alkyl and -NO₂; provided that R³ and R⁴ cannot both be hydrogen or hydroxy;

R⁸ and R⁹ are independently selected from the group consisting of hydrogen, C₃₋₆cycloalkyl, C₁₋₈alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C₆₋₁₄aryl optionally substituted with alkoxy, C₁₋₈alkylamino, C₁₋₈alkylheterocycle, heterocycle, heterocycleC₁₋₈alkyl, C₃₋₆cycloalkylC₁₋₈alkyl, and C₃₋₆cycloalkyl;

R¹⁰ is C₁₋₈alkyl;

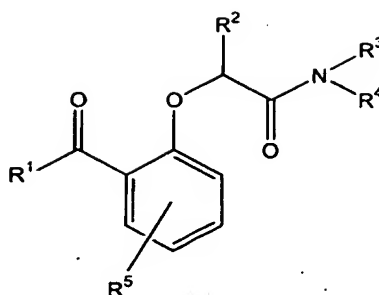
R¹¹ is C₁₋₈alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C₁₋₈alkyl, -S(O)₂NR⁸R⁹, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, and C₁₋₈alkyl;

R⁵ is hydrogen, halogen, C₁₋₈alkyl, -NO₂, -NH₂, C₁₋₈alkylamino, CF₃, or alkoxy; or a pharmaceutically acceptable derivative thereof.

Preferred compounds of formula (ID) are those wherein X is O.

More preferred compounds of formula (ID) are those wherein X is O; R¹ is heterocycle; R² and R³ are hydrogen; R⁴ is heterocycle; and R⁵ is halogen; or a pharmaceutically acceptable derivative thereof.

In a further aspect of the present invention there is provided compounds of formula (II):



(II)

wherein:

R^1 is C_{6-14} aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8} alkyl, C_{1-8} alkylamino, alkoxy, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{6-14} aryl, C_{2-6} alkenyl, $-CN$, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6} alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6} alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6} cycloalkyl, and heterocycle;

R^6 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6} cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8} alkyl;

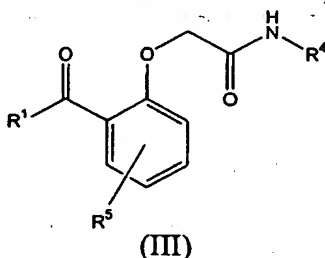
R^3 and R^4 form a heterocycle which may be optionally substituted with C_{6-14} aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8} alkyl and $-NO_2$;

provided that when R^1 is unsubstituted C_{6-14} aryl, then R^3R^4 is substituted.

R^5 is hydrogen, halogen, C_{1-8} alkyl, $-NO_2$, $-NH_2$, C_{1-8} alkylamino, CF_3 , or alkoxy; or a pharmaceutically acceptable derivative thereof.

Preferred compounds of formula (II) are those wherein R^1 is C_{6-14} aryl which is substituted with halogen; R^2 is hydrogen; R^3 and R^4 form a heterocycle which may be optionally substituted with C_{6-14} aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8} alkyl and $-NO_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

A further aspect of the present invention features compounds of formula (III):



wherein:

R^1 is C_{6-14} aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8} alkyl, C_{1-8} alkylamino, alkoxy, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{6-14} aryl C_{2-6} alkenyl, $-CN$, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6} alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6} alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6} cycloalkyl, and heterocycle; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8} alkyl, $-CN$, C_{6-14} aryl C_{1-8} alkyl and heterocycle;

R^6 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6} cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxy C_{1-8} alkyl, halogen, C_{1-8} alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$; or C_{6-14} aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8} alkyl, hydroxy C_{1-8} alkyl, $-CN$, $-NO_2$, C_{1-8} alkylamino, heterocycle C_{1-8} alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-S(O)_2NHR^{11}$, $S(O)_2R^{11}$, $OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycle C_{2-6} alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8} alkyl, and $-C(O)OR^{11}$, and C_{1-8} alkyl which may be optionally substituted with one or more substituents selected from the group consisting of $-CN$ and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^8 and R^9 are independently selected from the group consisting of hydrogen; C_{3-6} cycloalkyl; C_{1-8} alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14} aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8} alkylheterocycle, heterocycle, heterocycle C_{1-8} alkyl, C_{3-6} cycloalkyl C_{1-8} alkyl, and C_{3-6} cycloalkyl; or $-C(O)NH_2$;

R^{10} is C_{1-8} alkyl;

R^{11} is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8} alkyl, alkoxy, $-S(O)_2NR^8R^9$, $-NR^8R^9$ and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8} alkyl;

R^5 is hydrogen; halogen; C_{1-8} alkyl; $-NO_2$; $-NH_2$; C_{1-8} alkylamino; CF_3 , or alkoxy; or a pharmaceutically acceptable derivative thereof, provided that:

(a) when R^4 is C_{6-14} aryl substituted with OR^{11} wherein R^{11} is NR^8R^9 wherein R^8 and R^9 are C_{1-8} alkyl, and R^1 is C_{6-14} aryl, then R^1 cannot be substituted in the para position, and

(b) R^1 and R^4 cannot both be unsubstituted.

Preferred compounds of formula (III) are those wherein R^1 is C_{6-14} aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8} alkyl, $-CN$, $-SR^6$, $-S(O)_2R^6$; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8} alkyl, $-CN$, and C_{6-14} aryl C_{1-8} alkyl; R^6 is C_{1-8} alkyl, optionally substituted with halogen; R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, $-NH_2$, or heterocycle; R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, halogen, C_{1-8} alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$; or C_{6-14} aryl substituted with one or more substituents selected from the group consisting of hydroxy, $-CF_3$, C_{1-8} alkyl, hydroxy C_{1-8} alkyl, $-CN$, $-NO_2$, $-C(O)NH_2$, $-S(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8} alkyl; R^8 and R^9 are the same or different and are selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkylheterocycle, heterocycle, and C_{3-6} cycloalkyl; R^{10} is C_{1-8} alkyl; R^{11} is C_{1-8} alkyl, optionally substituted with $-S(O)_2NR^8R^9$; and R^5 is halogen or $-NO_2$; or a pharmaceutically acceptable derivative thereof.

More preferred compounds of formula (III) are those wherein R^1 is C_{6-14} aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8} alkyl, and $-CN$; R^4 is C_{6-14} aryl substituted with one or more substituents selected from the group consisting of halogen, C_{1-8} alkyl, $-CN$, $-NO_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-NS(O)_2R^7$, wherein R^7 is $-NH_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

The present invention further features compounds of formula (I), wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8} alkyl, C_{1-8} alkylamino, alkoxy, C_{3-6} cycloalkyl C_{2-6} alkenyl, C_{6-14} aryl C_{2-6} alkenyl, $-CN$, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6} alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6} alkynyl which may be optionally substituted with a substituent

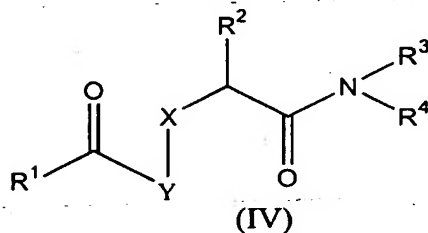
selected from the group consisting of hydroxy, halogen, aryl, C₃₋₆cycloalkyl, and heterocycle;

R² is hydrogen;

R³ is hydrogen;

- 5 R⁴ is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, -CF₃, or C₁₋₈alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, -CF₃, C₁₋₈alkyl, hydroxyC₁₋₈alkyl, -CN, -NO₂, C₁₋₈alkylamino, heterocycleC₁₋₈alkyl, -C(O)NH₂, -S(O)R⁷, -S(O)₂R⁷, -C(O)R⁷, -NS(O)₂R⁷, -S(O)₂NR⁸R⁹, -S(O)₂NHR¹¹, -SO₂R¹¹, -OR¹¹,
10 , -C(O)R¹¹, -C(O)NR¹¹, -C(O)OR¹¹, -NR¹¹, -NC(O)R¹¹, heterocycleC₂₋₆alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C₁₋₈alkyl, and C(O)OR¹¹, and C₁₋₈alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with -C(O)R¹¹;
- 15 R⁵ is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C₁₋₈alkyl, -NO₂, -NH₂, C₁₋₈alkylamino, CF₃, or alkoxy;
- R¹¹ is C₁₋₈alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C₁₋₈alkyl, -S(O)₂NR⁸R⁹, -NR⁸R⁹, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of
20 oxo and C₁₋₈alkyl; or a pharmaceutically acceptable derivative thereof.

The present invention also features compounds of formula (IV)



25

wherein:

X is C, O, or N;

- 30 Y is heterocycle optionally substituted with one or more substituents selected from the group consisting of halogen, C₁₋₈alkyl, -NO₂, -NH₂, C₁₋₈alkylamino, -CF₃, or alkoxy;

R^1 is C_{1-8} alkyl; C_{3-6} cycloalkyl; C_{6-14} aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8} alkyl, C_{1-8} alkylamino, C_{3-6} cycloalkyl C_{2-6} alkenyl, C_{6-14} aryl C_{2-6} alkenyl, $-CN$, $-NO_2$, $-NH_2$,
 5 $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6} alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6} alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6} cycloalkyl, and heterocycle; or heterocycle, optionally substituted with one or more
 10 substituents selected from the group consisting of C_{1-8} alkyl, $-CN$, C_{6-14} aryl C_{1-8} alkyl and heterocycle;

R^6 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from
 15 the group consisting of hydroxy, halogen, aryl, C_{3-6} cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8} alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxy C_{1-8} alkyl, halogen, C_{1-8} alkyl, OR^{11} and $-SR^{10}N(R^{10})_2$; or C_{6-14} aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8} alkyl, hydroxy C_{1-8} alkyl, $-CN$, $-NO_2$, C_{1-8} alkylamino, heterocycle C_{1-8} alkyl,
 25 $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NSO_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycle C_{2-6} alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8} alkyl, and $C(O)OR^{11}$, and C_{1-8} alkyl which may be optionally substituted with one or more substituents selected from the group consisting of $-CN$ and heterocycle, optionally substituted with $-C(O)R^{11}$; provided that R^3 and R^4 cannot
 30 both be hydrogen or hydroxy;

R^8 and R^9 are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkylamino, C_{1-8} alkylheterocycle, heterocycle, and C_{3-6} cycloalkyl;

R¹⁰ is C₁₋₈alkyl;

R¹¹ is C₁₋₈alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C₁₋₈alkyl, -SO₂NR⁸R⁹, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C₁₋₈alkyl;

R⁵ is hydrogen, halogen, C₁₋₈alkyl, -NO₂, -NH₂, C₁₋₈alkylamino, CF₃, or alkoxy; or a pharmaceutically acceptable derivative thereof.

Preferred compounds of formula (IV) are compounds wherein Y is a heterocycle substituted with one or more substituents selected from the group consisting of halogen, C₁₋₈alkyl, -NO₂, -NH₂, C₁₋₈alkylamino, -CF₃, or alkoxy; or a pharmaceutically acceptable derivative thereof. More preferred compounds of formula (IV) are compounds wherein X is O. Most preferred compounds of formula (IV) are those wherein X is O and Y is a heterocycle substituted with one or more substituents selected from the group consisting of halogen, C₁₋₈alkyl, -NO₂, -NH₂, C₁₋₈alkylamino, -CF₃, or alkoxy; or a pharmaceutically acceptable derivative thereof.

Preferred compounds of the present invention include:

2-[2-(1-benzothiophen-2-ylcarbonyl)-4-chlorophenoxy]-N-phenylacetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1H-imidazol-1-yl)phenyl]acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1λ⁴,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1H-1,2,4-triazol-1-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(4-morpholinyl)phenyl]acetamide;

N-[4-(aminosulfonyl)phenyl]-2-(2-benzoyl-4-chlorophenoxy)acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[(1,3-thiazol-2-ylamino)sulfonyl]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(4-methyl-1-piperazinyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(hydroxymethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[(methylamino)sulfonyl]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1,1-dioxo-1lambda~6~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[2-methyl-4-(4-morpholinyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[3-(dimethylamino)propoxy]-2-methylphenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-(1H-indazol-5-yl)acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(4-morpholinyl)propoxy]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[3-(1H-imidazol-1-yl)propoxy]-2-methylphenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-(1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-{2-methyl-4-[3-(4-morpholinyl)propoxy]phenyl}acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(1-oxo-1lambda~4~,4-thiazinan-4-yl)propoxy]phenyl}acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(2-benzoyl-4-chlorophenoxy)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]acetamide;

2-[2-(1-benzofuran-2-ylcarbonyl)-4-chlorophenoxy]-N-phenylacetamide

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-phenylacetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(2-furoyl)phenoxy]acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-(1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3-furoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-[4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-{4-chloro-2-[(1-methyl-1H-pyrrol-2-yl)carbonyl]phenoxy}-N-phenylacetamide;

2-(4-chloro-2-{[5-(2-pyridinyl)-2-thienyl]carbonyl}phenoxy)-N-phenylacetamide;

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-pyridinylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(2-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(4-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[2-(2-bromobenzoyl)-4-chlorophenoxy]acetamide;

2-{4-chloro-2-[(5-methyl-3-isoxazolyl)carbonyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

5 2-[4-chloro-2-(3-fluorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-chlorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

10 N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

15 N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-fluorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chlorobenzoyl)phenoxy]acetamide;

20 2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}acetamide;

25 2-{4-chloro-2-[3-(trifluoromethyl)benzoyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

30 2-[2-(3-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

35 N-[4-(aminosulfonyl)-2-methylphenyl]-2-[2-(3-bromobenzoyl)-4-chlorophenoxy]acetamide;

2-[4-chloro-2-(3-methylbenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

40 2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-pyridinylcarbonyl)phenoxy]acetamide;

45 2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(1-methyl-1H-imidazol-2-yl)carbonyl]phenoxy}acetamide;

5 N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

10 N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide

15 N-(1,3-benzothiazol-6-yl)-2-(2-benzoyl-4-chlorophenoxy)acetamide

2-(4-chloro-2-{3-[(trifluoromethyl)sulfanyl]benzoyl}phenoxy)-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide

20 2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

25 2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1 lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide;

30 N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

N-(1,3-benzothiazol-6-yl)-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide

35 2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-(2-methyl-1,3-benzothiazol-5-yl)acetamide

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(4-chloro-2-{3-[(trifluoromethyl)sulfanyl]benzoyl}phenoxy)acetamide;

40 N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(methylsulfonyl)phenyl]acetamide;

45 N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-(2-cyclopentylethynyl)benzoyl]phenoxy}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(5-methyl-1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-(2-phenylethynyl)benzoyl]phenoxy} acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

N-(1,2-benzisothiazol-5-yl)-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-1-(2,3-dihydro-1H-indol-1-yl)-1-ethanone;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

N-{4-[3-(aminosulfonyl)propoxy]-2-methylphenyl}-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide;

2-{2-[3,5-bis(trifluoromethyl)benzoyl]-4-chlorophenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{2-[(5-bromo-3-pyridinyl)carbonyl]-4-chlorophenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(6-methyl-1,3-benzothiazol-5-yl)acetamide;

N-{4-[3-(aminosulfonyl)propoxy]-2-methylphenyl}-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy} acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(4-chloro-2-{3-
[(trifluoromethyl)sulfonyl]benzoyl}phenoxy)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[4-(1,3-thiazol-2-yl)phenyl]acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[4-(1,3-oxazol-2-yl)phenyl]acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-{4-[(3-hydroxypropyl)sulfonyl]-2-
methylphenyl}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(2-methyl-4-{3-
[(methylamino)sulfonyl]propoxy}phenyl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(4-{3-
[(dimethylamino)sulfonyl]propoxy}-2-methylphenyl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{2-[(5-bromo-3-pyridinyl)carbonyl]-4-
chlorophenoxy}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-{4-[3-(1H-imidazol-1-
yl)propoxy]-2-methylphenyl}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-{2-methyl-4-[(E)-4-(1-
pyrrolidinyl)-1-butenyl]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-
fluorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-
methylbenzoyl)phenoxy]acetamide;

N-[6-(aminosulfonyl)-4-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-
methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-
cyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-
dimethylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-
ethylbenzoyl)phenoxy]acetamide;

2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]-N-{4-[3-(2,5-dihydro-1H-pyrrol-1-
yl)propoxy]-2-methylphenyl}acetamide hydrochloride;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-
methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide;

5 *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(6-cyano-2-pyridinyl)carbonyl]phenoxy} acetamide;

N-[6-(aminosulfonyl)-2-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

10 *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dicyanobenzoyl)phenoxy]acetamide;

15 *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-cyano-5-(trifluoromethyl)benzoyl]phenoxy} acetamide;

and pharmaceutically acceptable derivatives thereof.

20 Preferred compounds of the present invention include compound number 7, 32, 33, 36, 38, 44, 45, 49, 51, 52, 61, 65, 66, 71, 75, 76, 111, 112, 115, 118, 119, 128, 129, 171, 172, 191, 192, 199, 200, 206, 207, 224, 225, 232, 233, 235, 236, 246, 247, 253, 254, 255, 256, 259, 260, 261, 262, 264, 265, 267, 268, 288, 289, 290, 409, 412, 428, 430, 431, 433, 491, 564, 587, 475, 478, 498, 593, 483, 637, 503, 601, 658 and pharmaceutically acceptable derivatives thereof.

25 More preferred compounds of the present invention are selected from the group consisting of *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-fluoro-5-(trifluoromethyl)benzoyl)acetamide; *N*-{4-[3-(aminosulfonyl)propoxy]-2-methylphenyl}-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy} acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-fluorobenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide, *N*-[6-(aminosulfonyl)-4-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-cyanobenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dimethylbenzoyl)phenoxy]acetamide,

30 *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-ethylbenzoyl)phenoxy]acetamide, 2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]-*N*-{4-[3-(2,5-dihydro-1*H*-pyrrol-1-yl)propoxy]-2-methylphenyl} acetamide hydrochloride, *N*-

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[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-methylbenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-[(6-cyano-2-pyridinyl)carbonyl]phenoxy]acetamide, *N*-[6-(aminosulfonyl)-2-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dicyanobenzoyl)phenoxy]acetamide and pharmaceutically acceptable derivatives thereof.

Compounds of the present invention that are advantageous are those wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14} aryl substituted with C_{1-8} alkyl, in particular methyl, in addition to one or more other substituents as defined above.

The term "alkyl", alone or in combination with any other term, refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isoamyl, *n*-hexyl and the like.

The term "alkenyl," alone or in combination with any other term, refers to a straight-chain or branched-chain alkyl group with at least one carbon-carbon double bond. Examples of alkenyl radicals include, but are not limited to, ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, hexenyl, hexadienyl and the like.

The term "alkynyl" refers to hydrocarbon groups of either a straight or branched configuration with one or more carbon-carbon triple bonds which may occur in any stable point along the chain, such as ethynyl, propynyl, butynyl, pentynyl, and the like.

The term "alkoxy" refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy and the like.

The term "aryl," alone or in combination with any other term, refers to a carbocyclic aromatic radical (such as phenyl or naphthyl) containing the specified number of carbon atoms, preferably from 6-14 carbon atoms, and more preferably from 6-10 carbon atoms. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl, indanyl, azulenyl, fluorenyl, anthracenyl and the like.

The term "heterocycle" or "heterocyclic" as used herein, refers to a 3-to 7- membered monocyclic heterocyclic ring or 8-to 11- membered bicyclic heterocyclic ring which is either saturated, partially saturated or unsaturated, and which may be optionally benzofused if monocyclic. Each heterocycle consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any carbon or heteroatom which results in the creation of a stable structure. Preferred heterocycles include 5-7 membered monocyclic heterocycles and 8-10 membered bicyclic heterocycles. Examples of such groups include imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, indazolyl, indazolinolyl, perhydropyridazyl, pyridazyl, pyridyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, pyranyl, pyrazolinyl, piperazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, oxazolyl, benzoxazolyl, oxopiperidinyl, oxopyrrolidinyl, oxoazepinyl, azepinyl, isoxozolyl, isothiazolyl, furazanyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thiadiazoyl, dioxolyl, dioxinyl, oxathieryl, benzodioxolyl, dithiolyl, thiophenyl, tetrahydrothiophenyl, sulfolanyl, dioxanyl, dioxolanyl, tetrahydrofurodihydrofuranyl, tetrahydropyranodihydrofuranyl, dihydropyranyl, tetrahydrofurofuranyl and tetrahydropyranofuranyl.

Preferred heterocycles include imidazolidinyl, indazolyl, pyrrolidinyl, thiamorpholinyl, thiophenyl, furyl, benzofuranyl, thiazolyl, oxazolyl, pyrrolyl, indolinolyl, benzthiazolyl, pyridinolyl, quinolinoyl, and benzothiophenyl.

The term "halogen" refers to a radical of fluorine, chlorine, bromine or iodine.

The term "pharmaceutically effective amount" refers to an amount effective in treating a virus infection, for example an HIV infection, in a patient either as monotherapy or in combination with other agents. The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in a patient, or the improvement of an ascertainable measurement associated with a particular disorder, and may include the suppression of symptom recurrence in an asymptomatic patient such as a patient in whom a viral infection has become latent. The term "prophylactically effective amount" refers to an amount effective in preventing a virus infection, for example an HIV infection, or preventing the occurrence of symptoms of such an infection, in a patient. As used herein, the term "patient" refers to a mammal, including a human.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the antiviral agent.

As used herein, the compounds according to the invention are defined to include pharmaceutically acceptable derivatives thereof. A "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

Pharmaceutically acceptable salts of the compounds according to the invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g., magnesium), ammonium and NW_4^+ (wherein W is C_{1-4} alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts or organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ , NH_4^+ , and NW_4^+ (wherein W is a C_{1-4} alkyl group).

Esters of the compounds according to the invention are independently selected from the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters
5 advantageously comprises a phenyl group.

Any reference to any of the above compounds also includes a reference to a pharmaceutically acceptable salts thereof.

10 In a further aspect of the invention there are provided the compounds according to the invention for use in medical therapy particularly for the treatment or prophylaxis of viral infections such as an HIV infection. Compounds according to the invention have been shown to be active against HIV infections, although these compounds may be active against HBV infections as well.

15 The compounds according to the invention are particularly suited to the treatment or prophylaxis of HIV infections and associated conditions. Reference herein to treatment extends to prophylaxis as well as the treatment of established infections, symptoms, and associated clinical conditions such as AIDS related complex (ARC), Kaposi's sarcoma, and AIDS dementia.
20

According to a particular embodiment of the present invention, there is provided a method of treatment of HIV mutant viruses that exhibit NNRTI drug resistance by administering a therapeutically effective amount of a compound of the present invention
25 or a pharmaceutically acceptable derivative thereof to a mammal, in particular a human. In particular, the compounds of the present invention may be used to treat wild-type HIV-1 as well as several resistance mutations, for example, K103N, L100I, or Y181C.

According to another aspect, the present invention provides a method for the treatment
30 or prevention of the symptoms or effects of a viral infection in an infected animal, for example, a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a compound according to the invention. According to

a particular embodiment of this aspect of the invention, the viral infection is a retroviral infection, in particular an HIV infection. A further aspect of the invention includes a method for the treatment or prevention of the symptoms or effects of an HBV infection.

5 The compounds according to the invention may also be used in adjuvant therapy in the treatment of HIV infections or HIV-associated symptoms or effects, for example Kaposi's sarcoma.

10 The present invention further provides a method for the treatment of a clinical condition in an animal, for example, a mammal including a human which clinical condition includes those which have been discussed in the introduction hereinbefore, which comprises treating said animal with a therapeutically effective amount of a compound according to the invention. The present invention also includes a method for the treatment or prophylaxis of any of the aforementioned infections or conditions.

15 In yet a further aspect, the present invention provides the use of a compound according to the invention in the manufacture of a medicament for the treatment or prophylaxis of any of the above mentioned viral infections or conditions.

20 The above compounds according to the invention and their pharmaceutically acceptable derivatives may be employed in combination with other therapeutic agents for the treatment of the above infections or conditions. Combination therapies according to the present invention comprise the administration of at least one compound of the present invention or a pharmaceutically acceptable derivative thereof and at least one other
25 pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered simultaneously in either the same or different pharmaceutical formulations or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Preferably the combination
30 therapy involves the administration of one compound according to the invention and one of the agents mentioned herein below.

Examples of such further therapeutic agents include agents that are effective for the treatment of viral infections or associated conditions such as (1 alpha, 2 beta, 3 alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514], oxetanocin-G (3,4-bis-(hydroxymethyl)-2-oxetanosyl]guanine), acyclic nucleosides (e.g. acyclovir, valaciclovir, famciclovir, ganciclovir, penciclovir), acyclic nucleoside phosphonates (e.g. (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC), PMEA, ribonucleotide reductase inhibitors such as 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl] thiocarbonohydrazone, 3'azido-3'-deoxythymidine, other 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-didehydrothymidine, protease inhibitors such as indinavir, ritonavir, nelfinavir, amprenavir, oxathiolane nucleoside analogues such as (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine) or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), ribavirin, 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), tat inhibitors such as 7-chloro-5-(2-pyrrolyl)-3H-1,4-benzodiazepin-2-(H)one (Ro5-3335), 7-chloro-1,3-dihydro-5-(1H-pyrrol-2yl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429), interferons such as α -interferon, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyradamole; pentoxifylline, N-acetylcysteine (NAC), Procysteine, α -trichosanthin, phosphonoformic acid, as well as immunomodulators such as interleukin II or thymosin, granulocyte macrophage colony stimulating factors, erythropoietin, soluble CD₄ and genetically engineered derivatives thereof, or other non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine (BI-RG-587), loviride (α -APA) and delavuridine (BHAP), and phosphonoformic acid, and 1,4-dihydro-2H-3,1-benzoxazin-2-ones NNRTIs such as (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (L-743,726 or DMP-266), and quinoxaline NNRTIs such as isopropyl (2S)-7-fluoro-3,4-dihydro-2-ethyl-3-oxo-1(2H)-quinoxalinecarboxylate (HBY1293).

The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

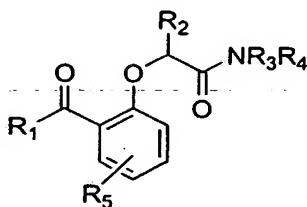
More preferably the combination therapy involves the administration of one of the above mentioned agents and a compound within one of the preferred or particularly preferred sub-groups within formulae (I) – (IV) (including IA, IB, IC and ID) as described above. Most preferably the combination therapy involves the joint use of one of the above named agents together with one of the compounds of the present invention specifically named herein.

The present invention further includes the use of a compound according to the invention in the manufacture of a medicament for simultaneous or sequential administration with at least one other therapeutic agent, such as those defined hereinbefore.

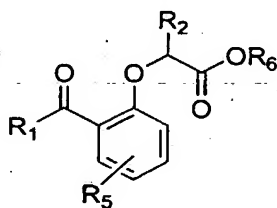
The compounds of the present invention may be synthesized by the following methods or by any method known in the art.

The compounds of the present invention may be prepared according to representative Schemes I-XXXIV, which are presented below. The compounds, which may be prepared according to these schemes, are not limited by the compounds contained in the schemes or by any particular substituents used in the schemes for illustrative purposes.

Compounds of formula (I) wherein R_1 is hereinbefore defined, can be readily prepared from compounds of formula IV and V wherein R_1 , R_2 , R_3 , R_4 , and R_5 are as hereinbefore defined and R_6 is hydrogen, using suitable coupling conditions known in the art.



I



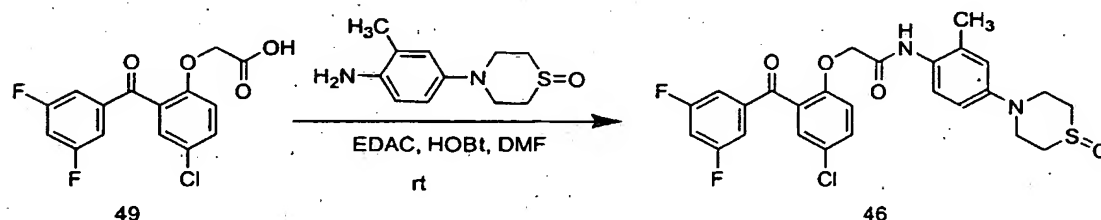
IV



V

For example, compounds of formula IV can be allowed to react with compounds of formula V in the presence of a suitable dehydrating agent, such as a carbodiimide, dicyclohexylcarbodiimide (DCC) for example, or more preferably 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC). In addition, the presence of a suitable activating agent, such as 1-hydroxybenztriazole (HOBt), is usually required to promote efficient coupling of the carboxylic acid to the appropriate amine. These reactions are typically carried out in an aprotic solvent such as acetonitrile, tetrahydrofuran or more preferably N,N-dimethylformamide (DMF), at temperatures from 0 °C to 150 °C, most preferably at ambient temperatures. For example, carboxylic acid 49 (Scheme I) is allowed to react with amine 399 in DMF and in the presence of EDAC and HOBt at ambient temperature to provide compound 46.

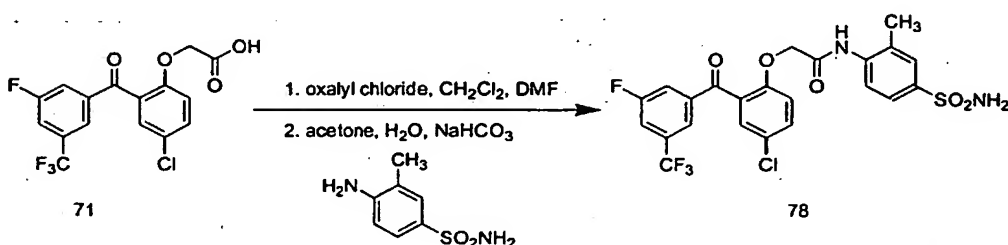
Scheme I



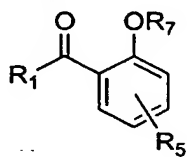
Alternatively, compounds of formula IV, wherein R_1 , R_2 , and R_5 are as hereinbefore defined, can first be converted to the corresponding acid chloride which is then allowed to react with compounds of formula V, wherein R_3 and R_4 are as hereinbefore defined, to afford compounds of (I). The preparation of the desired acid chloride can be accomplished by methods well-known in the art. The carboxylic acids can be allowed to react with a suitable dehydrating agent such as thionyl chloride or more preferably oxalyl chloride. These reactions are typically performed in an aprotic solvent such as acetonitrile or pyridine or a chlorinated solvent such as chloroform or more preferably dichloromethane. The corresponding acid chlorides are not typically isolated in pure form, but instead are allowed to react directly with compounds of formula V. Most often, reactions of the acid chlorides are performed in an aprotic solvent such as acetonitrile or chloroform, or more preferably in acetone. In addition, the presence of a compound capable of acting as a base such as triethylamine or pyridine, or more preferably sodium bicarbonate, is required in order to obtain sufficient yields of the coupling products. When

inorganic bases such as sodium bicarbonate are used, the addition of a small amount of water to the reaction mixture promotes an efficient coupling reaction. For example, carboxylic acid **71** (Scheme II) is allowed to react with oxalyl chloride in dichloromethane and in the presence of a catalytic amount of DMF to afford the corresponding acid chloride. The acid chloride is then allowed to react with amine **466** in a mixture of acetone and water and in the presence of an excess of sodium bicarbonate to provide compound **78**

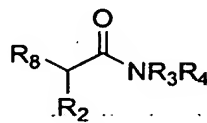
Scheme II



Lastly, compounds of formula I in which R₁ – R₅ are as hereinbefore defined, can be readily prepared by reaction of compounds of formula VI, wherein R₇ is hydrogen with compounds of formula VII wherein R₂, R₃ and R₄ are as hereinbefore defined, and R₈ is a suitable leaving group such as a halogen, preferably chlorine or bromine, or a methanesulfonate or para-toluenesulfonate ester.



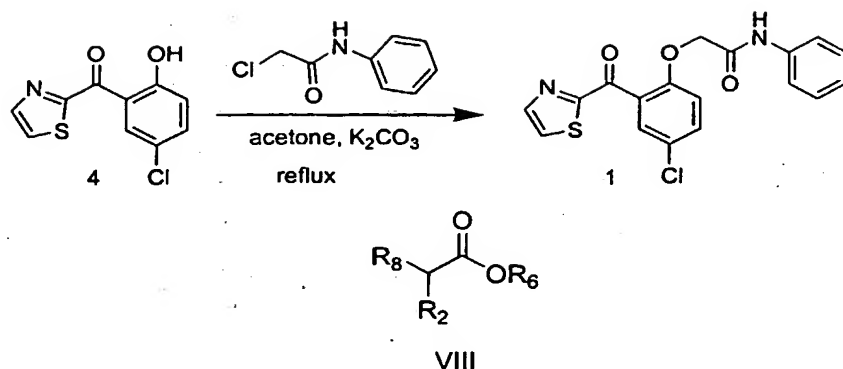
VI



VII

The alkylation of compounds of formula VI by compounds of formula VII are typically performed in an aprotic solvent such as acetonitrile, DMF or more preferably in acetone. In addition, the presence of a compound capable of acting as a base such as triethylamine, pyridine, or more preferably sodium carbonate, is usually required to promote efficient reaction. Furthermore, the reactions are typically carried out at elevated temperatures in the range of 40-100 °C. For example, phenol **4** (Scheme III) is allowed to react with 2'-chloroacetanilide in the presence of sodium carbonate in refluxing acetone to provide compound **1**.

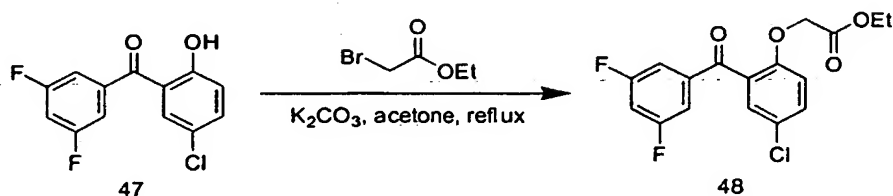
Scheme III



Compounds of formula IV, wherein R_1 , R_2 and R_5 are as hereinbefore defined and R_6 is C_{1-6} alkyl, can be prepared by reaction of compounds of formula VI, wherein R_1 and R_5 are as hereinbefore defined, and R_7 is hydrogen, with those of formula VIII, wherein R_6 is C_{1-6} alkyl, R_2 is as hereinbefore defined, and R_8 is a suitable leaving group such as a halogen, preferably chlorine or bromine, or a methanesulfonate or para-toluenesulfonate ester. Typically, the reactions are performed in an aprotic solvent such as acetonitrile, DMF, or more preferably acetone, and temperatures ranging from 40 °C to 100 °C. In addition, the presence of an excess of a base such as triethylamine, pyridine, or more preferably potassium carbonate, is usually required for efficient reaction. For example, phenol 47 (Scheme IV) is allowed to react with ethyl bromoacetate in refluxing acetone and in the presence of potassium carbonate to afford ester 48.

Compounds of formula VIII are either commercially available or can be prepared using literature methods that are known in the art.

Scheme IV

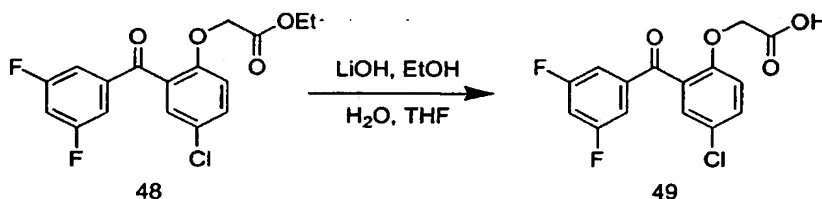


Compounds of formula IV, in which R_1 , R_2 and R_5 are as hereinbefore defined and R_6 is hydrogen can be prepared from compounds of formula IV in which R_1 , R_2 and R_5 are as hereinbefore defined and R_6 is C_{1-6} alkyl, by reaction with aqueous base or other suitable

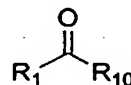
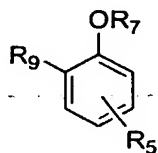
methods known in the art. A variety of inorganic bases can be used to affect the saponification of the esters of formula IV, such as sodium carbonate, sodium hydroxide or more preferably lithium hydroxide. Typically, these reactions are performed in water in addition to a solvent that is miscible with water and is capable of dissolving the compounds of formula IV such as tetrahydrofuran, methyl alcohol or ethyl alcohol.

For example, ester **48** (Scheme V) is allowed to react with lithium hydroxide in a mixture of THF, water, and ethanol to afford carboxylic acid **49**.

Scheme V



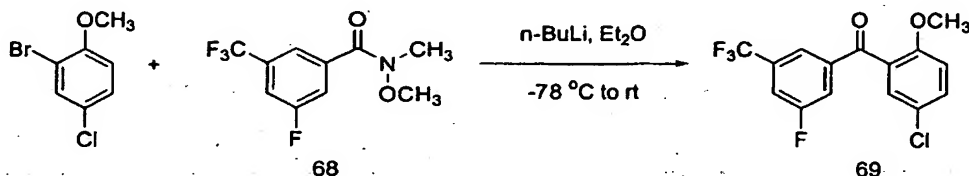
Below are schemes showing the preparation of compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined, and R_7 is either hydrogen or methyl. Compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is methyl, can be prepared by reaction of compounds of formula IX, wherein R_5 is as hereinbefore defined, and R_7 is methyl with those of formula X, wherein R_1 and R_{10} are as hereinbefore defined, with the further stipulation that these groups are chemically compatible with the reaction conditions, R_7 is methyl, R_9 is a halogen, preferably bromine or iodine, and R_{10} is N,O-dimethylhydroxylamino.



Typically, compounds of formula IX are treated with an agent capable of effecting a halogen-metal exchange reaction, such as sec-butyl lithium, methyl lithium, tert-butyl lithium, or more preferably n-butyl lithium. The halogen-metal exchange can be performed in an ethereal solvent such as THF, dioxane or more preferably diethyl ether, and at low temperatures ranging from -100 °C to 0 °C, most preferably -78 °C. When the halogen-metal exchange reaction is complete, the resulting compounds of formula IX, in which R_9 is lithium, are allowed to react with compounds of formula X, again in an ethereal solvent and at low temperatures. For example, 2-bromo-4-chloroanisole (Scheme

VI) in diethyl ether is treated with *n*-butyl lithium at -78°C . After 15 minutes at -78°C , the resulting lithium species is allowed to react with amide 68 to afford the desired ketone 69.

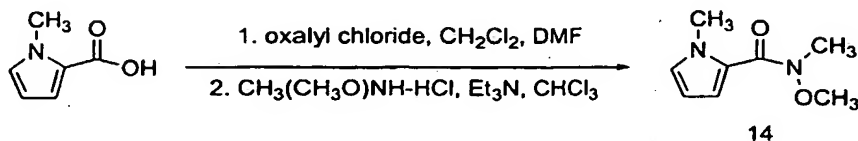
Scheme VI



Compounds of formula IX, in which R₅ is as hereinbefore defined, R₇ is methyl and R₉ is either bromine or iodine are either commercially available or can be prepared using literature methods known in the art.

Compounds of formula X, in which R₁ is as hereinbefore defined and R₁₀ is N,O-dimethylhydroxylamino, can be prepared from compounds of formula X in which R₁₀ is a suitable leaving group, preferably chlorine, by reaction with N,O-dimethylhydroxylamine in an aprotic solvent, preferably acetonitrile, chloroform or dichloromethane, and in the presence of a base, preferably triethylamine. Compounds of formula X in which R₁₀ is chlorine can be prepared from compounds of formula X, in which R₁₀ is hydroxy, using literature methods known in the art, such as reaction with oxalyl chloride in an aprotic solvent, preferably dichloromethane or chloroform and in the presence of a catalytic amount of DMF. For example, 1-methyl-2-pyrrolecarboxylic acid (Scheme VII) in dichloromethane is allowed to react with excess oxalyl chloride in the presence of a catalytic amount of DMF. The resulting acid chloride is not isolated in pure form, but instead is allowed to react with N,O-dimethylhydroxylamine in chloroform and in the presence of triethylamine, to afford amide 14.

Scheme VII

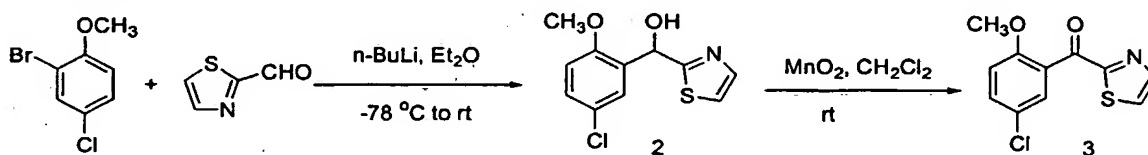


Alternatively, compounds of formula VI, in which R₁ and R₅ are as hereinbefore defined and R₇ is methyl can be prepared by reaction of compounds of formula IX with those of formula X, wherein R₁ and R₅ are as hereinbefore defined with the further stipulation that these groups are chemically compatible with the reaction conditions, R₇ is methyl, R₉ is a halogen, preferably bromine or iodine, and R₁₀ is N,O-dimethylhydroxylamino. Compounds of formula IX can be converted to a species in which R₉ is a magnesium halide, such as magnesium bromide or magnesium iodide, so-called Grignard reagents. The species containing the magnesium halide is then allowed to react with compounds of formula X, in which R₁₀ is N,O-dimethylhydroxylamino. These reactions are typically performed in ethereal solvents such as THF, dioxane or diethyl ether and at temperatures from 0 °C to 100 °C, preferably ambient temperature. The preparation of compounds of formula IX in which R₉ is a magnesium halide can be accomplished by literature methods known in the art. Typically, a compound of formula IX, in which R₉ is either bromine or iodine, is allowed to react with elemental magnesium in an aprotic, ethereal solvent.

Alternatively, compounds of formula VI, in which R₁ and R₅ are as hereinbefore defined and R₇ is methyl, can be prepared from compounds of formula IX, in which R₅ is as hereinbefore defined, R₇ is methyl and R₉ is a halogen, preferably bromine or iodine, by reaction with compounds of formula X, in which R₁ is as hereinbefore defined and R₁₀ is hydrogen, with the further stipulation that R₁ is chemically compatible with subsequent reaction conditions. Compounds of formula X, in which R₁ is as hereinbefore defined and R₁₀ is hydrogen, are either commercially available or can be prepared using literature methods known in the art. Compounds of formula IX, in which R₉ is either bromine or iodine, are first treated with an agent capable of effecting a halogen-metal exchange reaction, preferably n-butyl lithium, in an ethereal solvent, preferably diethyl ether, and at low temperatures, preferably - 78 °C. After the compound of formula IX, in which R₉ is lithium, has formed, it is allowed to react with compounds of formula X, in which R₁₀ is hydrogen, to afford an intermediate alcohol species. Subsequently, the intermediate alcohol can be treated with an agent capable of oxidizing the alcohol to a compound of formula VI, the preferred oxidizing agent being manganese (IV) oxide. Typically, the oxidation reactions are performed in an aprotic solvent, preferably chloroform or dichloromethane, and at ambient temperatures. For example, 2-bromo-4-chloroanisole was

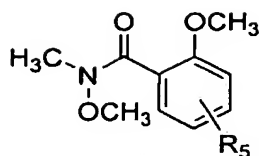
treated with n-butyl lithium in ether and at -78°C . The resulting lithio species is then allowed to react with 2-thiazolecarboxaldehyde to afford intermediate alcohol 2. Alcohol 2 is then allowed to react with an excess of manganese dioxide in dichloromethane at room temperature to afford ketone 3

5 **Scheme VIII**



Alternatively, compounds of formula VI, in which R₁ and R₅ are as hereinbefore defined and R₇ is methyl, can be prepared by reaction of compounds of formula IX with those of formula X, wherein R₁ and R₅ are as hereinbefore defined, with the further stipulation that these groups are chemically compatible with the reaction conditions, R₇ is methyl, R₉ is a halogen, preferably bromine or iodine, and R₁₀ is hydrogen. Compounds of formula IX can be converted to a species in which R₉ is a magnesium halide, such as magnesium bromide or magnesium iodide, so-called Grignard reagents. The species containing the magnesium halide is then allowed to react with compounds of formula X, in which R₁₀ is hydrogen, to afford an intermediate alcohol. These reactions are typically performed in ethereal solvents such as THF, dioxane or diethyl ether and at temperatures from 0°C to 100°C , preferably ambient temperature. The preparation of compounds of formula IX, in which R₉ is a magnesium halide, can be accomplished by literature methods known in the art. Typically, a compound of formula IX, in which R₉ is either bromine or iodine, is allowed to react with elemental magnesium, in an aprotic, ethereal solvent. The intermediate alcohol is then allowed to react with an agent capable of oxidizing it to the desired ketone, preferably manganese (IV) oxide, in an aprotic solvent, preferably dichloromethane or chloroform, and at ambient temperature.

Lastly, compounds of formula VI, in which R₁ and R₅ are as hereinbefore defined and R₇ is methyl, can be prepared by reaction of compounds of formula XII, in which R₅ is as hereinbefore defined, with compounds of formula XIII, in which R₁ is as hereinbefore defined, and R₁₁ is a halogen, preferably bromine or iodine, with the further stipulation that R₁ and R₅ are chemically compatible with subsequent chemical steps.



XII



XIII

Typically, compounds of formula XIII, in which R_{11} is a halogen, preferably iodine or bromine, are treated with an agent capable of effecting a halogen-metal exchange reaction, preferably n-butyl lithium, in an ethereal solvent, preferably diethyl ether and at low temperature, preferably -78°C .

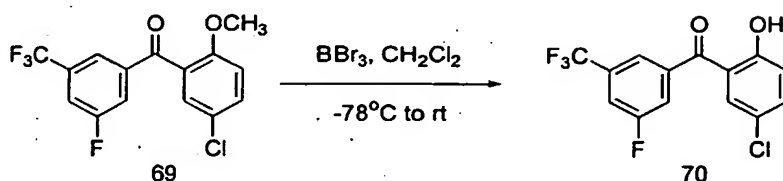
Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is methyl, can be prepared by reaction of compounds of formula XII with those of formula XIII, wherein R_1 and R_5 are as hereinbefore defined, with the further stipulation that these groups are chemically compatible with the reaction conditions, and R_{11} is a halogen, preferably bromine or iodine. Compounds of formula XIII can be converted to a species in which R_{11} is a magnesium halide, such as magnesium bromide or magnesium iodide, so-called Grignard reagents. The species containing the magnesium halide is then allowed to react with compounds of formula XII to afford the desired ketone. These reactions are typically performed in ethereal solvents such as THF, dioxane or diethyl ether and at temperatures from 0°C to 100°C , preferably ambient temperature. The preparation of compounds of formula XIII, in which R_{11} is a magnesium halide, can be accomplished by literature methods known in the art. Typically, a compound of formula XIII in which R_{11} is either bromine or iodine is allowed to react with elemental magnesium, in an aprotic, ethereal solvent.

Compounds of formula XIII, in which R_{11} is a halogen, preferably bromine or iodine, are either commercially available or can be prepared by literature methods.

Compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is hydrogen, can be prepared from compounds of formula VI, in which R_7 is methyl, by reaction with agents capable of demethylating aryl methyl ethers, with the stipulation that R_1 and R_5 are chemically stable under these reaction conditions. Among the agents which may be used for demethylating aryl methyl ethers are trimethylsilyl iodide, Lewis acids such as aluminum chloride, or more preferably boron tribromide. These reactions are typically conducted in aprotic solvents such as chloroform or dichloromethane and at temperatures from -78° to 100°C , preferably from -78°C to ambient temperature. For

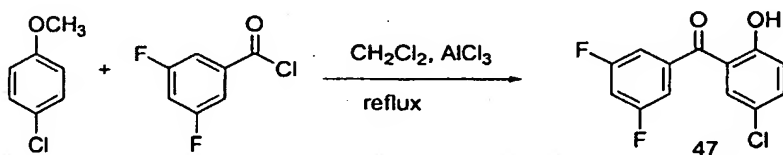
example, ketone **69** (Scheme IX) is allowed to react with an excess of boron tribromide in dichloromethane at -78°C to afford phenol **70**.

Scheme IX



Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined, and R_7 is hydrogen, can be prepared by reaction of compounds of formula IX, in which R_5 is as hereinbefore defined, R_9 is hydrogen and R_7 is methyl, with compounds of formula X, in which R_1 is as hereinbefore defined, and R_{10} is a halogen, preferably chlorine, with the further stipulation that R_1 and R_5 are chemically compatible with the reaction conditions. These reactions, typically called Friedel-Craft acylations, are performed in an aprotic solvent such as nitrobenzene, 1,2-dichloroethane, sulfolane, or more preferably dichloromethane, at temperatures ranging from 0°C to 150°C , preferably 35 - 60°C . In addition, the use of a compound which is capable of acting as a Lewis acid, such as titanium (IV) chloride, tin (IV) chloride, or more preferably aluminum chloride is required. For example, 4-chloroanisole (Scheme X) is allowed to react with 3,5-difluorobenzoyl chloride in refluxing dichloromethane in the presence of aluminum chloride to afford ketone **47**.

Scheme X

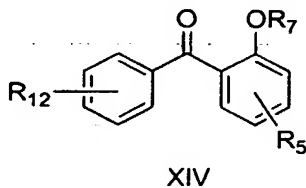


Compounds of formula X, in which R_1 is as hereinbefore defined, and R_{10} is a halogen, are either commercially available or can be prepared by literature methods. Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore described and R_7 is hydrogen, can be prepared from the reaction of compounds of formula IX, in which R_5 is as hereinbefore defined, and R_7 and R_9 are hydrogen, with compounds of formula X, in which R_1 is as hereinbefore defined and R_{10} is a halogen, preferably chlorine. These

reactions, typically called Fries rearrangements, are performed in an aprotic solvent, such as nitrobenzene, sulfolane or chloroform and at temperatures ranging from 0 °C to 150 °C. In addition, the reaction typically requires the presence of a compound capable of acting as a Lewis acid, such as aluminum chloride. Compounds of formula IX, in which R₅ is as
 5 hereinbefore defined, and R₆ and R₇ are hydrogen, are either commercially available or can be prepared by literature methods which are familiar to those skilled in the art.

Compounds of formula VI in which R₁ is C₆₋₁₄ aryl or C₆₋₁₄ heterocycle, substituted with C₂₋₈ alkenyl, can be prepared from compounds of formula XIV, wherein R₅ is as hereinbefore defined, R₇ is hydrogen, methyl or methylene carboxyl ester and R₁₂ is a
 10 group capable of undergoing a palladium-catalyzed reaction, such as bromine, iodine, or trifluoromethanesulfonate ester, by reaction with C₂₋₈ alkenes.

These reactions are typically conducted in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium, palladium dichloride bis(acetonitrile), or more preferably palladium acetate. The solvents for these reactions are typically aprotic solvents
 15 such as acetonitrile, or more preferably DMF. The reactions are usually performed at temperatures ranging from ambient temperature to 130 °C, preferably 50-90 °C. In addition, the presence of a base such as potassium or sodium carbonate, or triethylamine, is usually required. Lastly, reactions of some substrates may require the addition of a compound which is capable of stabilizing any intermediate palladium species. These
 20 compounds are most often triaryl arsine or phosphine derivatives, such as triphenylphosphine, or tri-ortho-tolylphosphine.



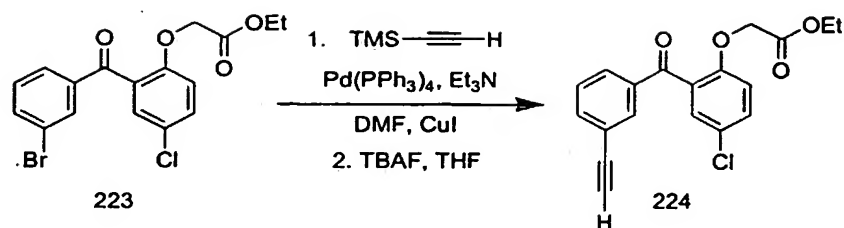
The C₂₋₈ alkenes used in these reactions are either commercially available or can be prepared using literature methods which are familiar to those skilled in the art.

Compounds of formula XIV in which R₇, and R₅ are as hereinbefore defined and R₁₂ is
 25 a group capable of undergoing a palladium-catalyzed reaction, such as bromine, iodine, or trifluoromethanesulfonate ester, are either commercially available or can be prepared by literature methods.

Compounds of formula VI in which R_1 is C_{6-14} aryl or C_{6-14} heterocycle, substituted with C_{2-8} alkyl, can be prepared from compounds of formula VI in which R_1 is C_{6-14} aryl, substituted with C_{2-8} alkenyl, by reaction with agents capable of selectively reducing the alkene bond. Among the agents that may be used to effect the desired reduction are
5 palladium on carbon and Raney nickel. In addition, the presence of a reducing agent such as ammonium formate or pressurized hydrogen gas is required. These reactions are typically performed in a solvent capable of dissolving the olefinic substrate such as ethyl acetate, acetone, methyl alcohol or ethyl alcohol.

Compounds of formula VI in which R_1 is C_{6-14} aryl or C_{6-14} heterocycle, substituted
10 with C_{2-8} alkynyl groups, can be prepared from compounds of formula XIV, in which R_5 is as hereinbefore described, R_7 is hydrogen, methyl or methylene carboxyl ester and R_{12} is a group capable of undergoing a palladium-catalyzed reaction, preferably iodine or bromine, by reaction with C_{2-8} alkynes. These reactions are typically performed in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium, palladium dichloride
15 bis(acetonitrile), or palladium acetate. The solvents for these reactions are typically aprotic solvents such as acetonitrile, or more preferably DMF. The reactions are usually performed at temperatures ranging from ambient temperature to 130°C , preferably $50-90^\circ\text{C}$. In addition, the presence of a base such as potassium or sodium carbonate, or triethylamine, is usually required. Furthermore, reactions of some substrates may require
20 the addition of a compound which is capable of stabilizing any intermediate palladium species. These compounds are most often triaryl arsine or phosphine derivatives, such as triphenylphosphine, or tri-ortho-tolylphosphine. Lastly, these reactions require the presence of a catalytic amount of copper (I) iodide. For example, ester 223 (Scheme XI) is allowed to react with trimethylsilylacetylene, in the presence of
25 tetrakis(triphenylphosphine)palladium, triethylamine and copper (I) iodide, to afford the intermediate trimethylsilyl-protected product. Treatment of the intermediate with tetrabutylammonium fluoride in THF provides compound 224

Scheme XI



The C₂₋₈ alkynes used in these reactions are either commercially available or can be prepared by literature methods familiar to those skilled in the art.

Compounds of formula VI in which R₁ is C₆₋₁₄ aryl or C₆₋₁₄ arylheterocycle substituted with an amino group, R₅ is as hereinbefore described, and R₇ is hydrogen, methyl or methylene carboxy ester can be prepared from compounds of formula VI, in which R₁ is C₆₋₁₄ aryl or C₆₋₁₄ arylheterocycle substituted with nitro, by reaction with a combination of agents which are capable of reducing a nitro functionality to an amino group. Among these combination of agents are a metal containing compound, such as elemental iron, palladium or Raney nickel and a reducing agent, such as ammonium formate, formic acid, hydrochloric acid or pressurized hydrogen gas. These reactions are typically performed in a solvent such as ethyl acetate, acetone, methyl alcohol or ethyl alcohol and at temperatures ranging from 20 °C to 100 °C, preferably ambient temperature.

Compounds of formula VI, in which R₁ is C₆₋₁₄ aryl or C₆₋₁₄ arylheterocycle, substituted with a nitro functionality, R₅ is as hereinbefore described and R₇ is hydrogen or methyl, can be prepared by methods previously described herein or by literature methods known in the art.

Compounds of formula VI, in which R₁ is C₆₋₁₄ aryl or C₆₋₁₄ arylheterocycle substituted with -SO₂R₁₃, where R₅ is as previously defined, R₇ is hydrogen, methyl or methylene carboxy ester and R₁₃ is C₁₋₈ alkyl, which is optionally substituted with hydroxy, alkylamino, or halogen, can be prepared from compounds of formula VI in which R₁ is C₆₋₁₄ aryl or C₆₋₁₄ arylheterocycle substituted with SR₁₃, by reaction with agents which are capable of oxidizing a sulfide to a sulfone. Among the agents which are capable of effecting the desired, selective oxidation are meta-chloroperbenzoic acid (m-CPBA), hydrogen peroxide in acetic acid and oxone. These reactions are typically conducted in solvents such as dichloromethane, chloroform, ethyl alcohol, water or a mixture of these solvents and in the temperature range from 0 °C to 100 °C.

Compounds of formula VI, in which R_1 is C_{6-14} aryl or C_{6-14} arylheterocycle substituted with $-SR_{13}$, wherein R_{13} is as previously described herein, can be prepared from commercially available material or by literature methods familiar to those skilled in the art.

5 Compounds of formula VI, in which R_1 is C_{6-14} aryl or C_{6-14} arylheterocycle substituted with nitrile, can be prepared from compounds of formula VI, in which R_1 is C_{6-14} aryl or C_{6-14} arylheterocycle substituted with a halogen, preferably bromine or iodine, by reaction with an agent or a combination of agents capable of replacing the halogen with a nitrile functional group. Among these agents are copper (I) cyanide or a palladium catalyst in
10 combination with an appropriate cyanide source such as potassium cyanide, sodium cyanide, or zinc cyanide. Among the palladium agents that can be employed for this transformation are tetrakis(triphenylphosphine)palladium, palladium acetate, or palladium dichloride bis(acetonitrile). These reactions are typically conducted in aprotic solvents such as acetonitrile, or more preferably DMF, and in the presence of phosphine ligand,
15 such as triphenylphosphine, and at temperatures from 20 °C to 150 °C, preferably 80-85 °C.

Compounds of formula VI, in which R_1 is as hereinbefore described, R_7 is hydrogen, methyl or methylene carboxy ester and R_5 is hydrogen, halogen, nitro, trifluoromethyl, C_{1-8} alkyl or alkoxy can be prepared from commercially available material using processes
20 described herein or by literature methods familiar to those skilled in the art.

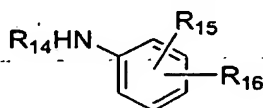
Compounds of formula VI, in which R_1 is as previously described, R_7 is hydrogen, methyl or methylene carboxy ester, and R_5 is amino, can be prepared from compounds of formula VI in which R_5 is nitro by reaction with agents or a combination of agents capable of reducing a nitro group to an amino functionality. Among these combination of agents
25 are a metal containing compound, such as elemental iron, palladium or Raney nickel and a reducing agent, such as ammonium formate, formic acid, hydrochloric acid or pressurized hydrogen gas. These reactions are typically performed in a solvent such as ethyl acetate, acetone, methyl alcohol or ethyl alcohol and at temperatures ranging from 20 °C to 100 °C, preferably ambient temperature.

30 Compounds of formula VI in which R_1 is as hereinbefore defined, R_7 is hydrogen, methyl or methylene carboxy ester, and R_5 is C_{1-8} alkylamino can be prepared from compounds of formula VI in which R_5 is amino, by reaction with agents capable of

selectively alkylating the amino group. Among these agents are alkyl halides, such as methyl iodide, alkylsulfonate esters or alkylaryl sulfonate esters. These reactions are typically performed in polar, aprotic solvents such as N-methylpyrrolidine or DMF and at temperatures ranging from ambient to 150 °C.

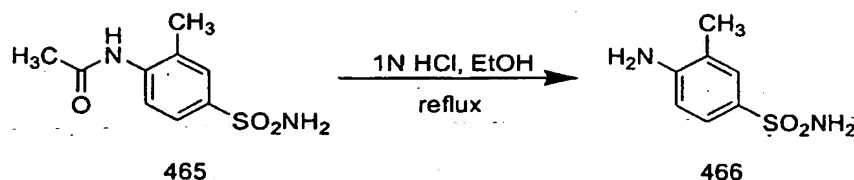
Compounds of formula V, in which R₃ and R₄, which may be the same or different, are hydrogen, hydroxy, C₁₋₈alkyl, heterocycle, C₆₋₁₄arylheterocycle or C₆₋₁₄aryl are commercially available or can be prepared by literature methods familiar to those skilled in the art.

Compounds of formula V, in which R₃ is hydrogen and R₄ is C₆₋₁₄aryl substituted with -SO₂NR₆R₇, wherein R₆ and R₇ are as hereinbefore defined, are either commercially available or can be prepared from compounds of formula XV, in which R₁₄ is a nitrogen protecting group, such as trifluoromethyl acetyl, or more preferably acetyl, R₁₅ is hydrogen, halogen, C₁₋₈alkyl, C₁₋₈alkoxy, nitro, nitrile, trifluoromethyl, and R₁₆ is -SO₂NR₆R₇, by reaction with either aqueous base or aqueous acid. These reactions are typically performed in a protic solvent such as water, methyl alcohol, ethyl alcohol or a mixture thereof, and at temperatures ranging from 25 °C to 100 °C, preferably 60-70 °C. For example, compound 465 (Scheme XII) is allowed to react with 1N aqueous hydrochloric acid solution in ethanol at reflux temperature to afford 466.



XV

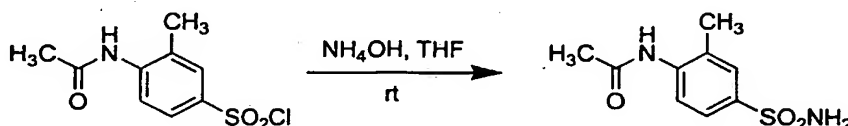
20 Scheme XII



Compounds of formula V, in which R₃ is hydrogen and R₄ is C₆₋₁₄aryl substituted with -SO₂NR₆R₇, wherein R₆ and R₇ are as hereinbefore defined, can be prepared from compounds of formula XV, in which R₁₄ is a nitrogen protecting group, such as trifluoromethyl acetyl, or more preferably acetyl, R₁₅ is hydrogen, halogen, C₁₋₈alkyl, C₁₋

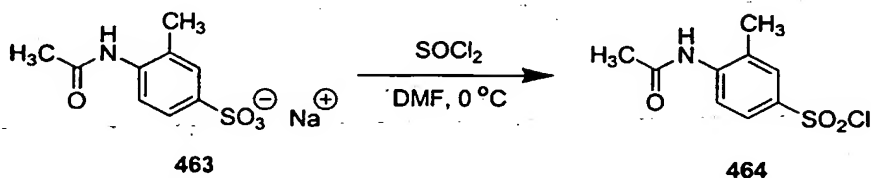
alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-\text{SO}_2\text{Cl}$, by reaction with an appropriate amine. These reactions are typically conducted in a solvent such as ethyl alcohol, THF or acetone and at temperatures from -10°C to 50°C , preferably $20-25^\circ\text{C}$. For example, sulfonyl chloride 464 (Scheme XIII) is allowed to react with ammonium hydroxide in THF at ambient temperature to afford sulfonamide 465.

Scheme XIII



Compounds of formula XV, in which R_{14} is a nitrogen protecting group, such as trifluoromethyl acetyl, or more preferably acetyl, R_{15} is hydrogen, halogen, C_{1-8} alkyl, C_{1-8} alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-\text{SO}_2\text{Cl}$, can be prepared from compounds of formula XV, in which R_{16} is $-\text{SO}_3\text{H}$ or a salt thereof, by reaction with an agent capable of converting a sulfonic acid or a salt thereof to a sulfonyl chloride. Among the agents that are capable of affecting this transformation are phosphorous oxychloride (POCl_3), or thionyl chloride. These reactions are conducted in an aprotic solvent such as DMF, and at temperatures from -10°C to 100°C , preferably 0°C . For example, compound 463 (Scheme XIV) is allowed to react with thionyl chloride in DMF at 0°C to provide sulfonyl chloride 464.

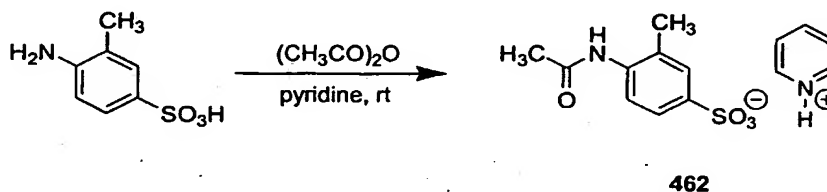
Scheme XIV



Compounds of formula XV, in which R_{14} is a nitrogen protecting group, such as trifluoromethyl acetyl, or more preferably acetyl, R_{15} is hydrogen, halogen, C_{1-8} alkyl, C_{1-8} alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-\text{SO}_3\text{H}$ or a salt thereof, can be prepared from compounds of formula XV, in which R_{14} is hydrogen, by reaction with an agent capable of selectively protecting the amino group. Among the reagents that are capable of affecting this transformation are trifluoroacetic anhydride, acetyl chloride, or more preferably acetic anhydride. These reactions are conducted in an aprotic solvent, such as acetonitrile, dichloromethane, chloroform, or more preferably pyridine, and at

temperatures from 0 °C to 100 °C, preferably ambient temperatures. For example, 2-aminotoluene-5-sulfonic acid (Scheme XV) is allowed to react with acetic anhydride in pyridine at ambient temperature to provide compound 462.

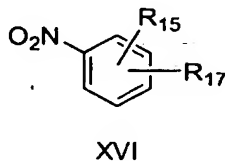
Scheme XV



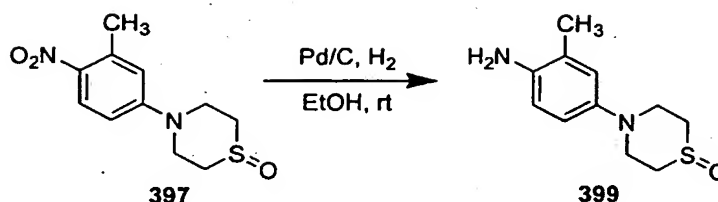
Compounds of formula XV, in which R_{14} is hydrogen, R_{15} is hydrogen, halogen, C_{1-8} -alkyl, C_{1-8} alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-SO_3H$ or a salt thereof, are commercially available or can be prepared by literature methods familiar to those skilled in the art.

Compounds of formula V in which R_3 is hydrogen and R_4 is C_{6-14} arylheterocycle substituted with $-SO_2$, $-S(O)$, or $C(O)$, can be prepared from compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8} alkyl, C_{1-8} alkoxy, nitro, nitrile, trifluoromethyl, and R_{17} is a heterocycle substituted with $-SO_2$, $-S(O)$, or $C(O)$, by reaction with an agent or a combination of agents capable of selectively reducing the nitro group to an amino group.

Among the agents capable of affecting this transformation are palladium on carbon in combination with hydrogen gas, Raney nickel in combination with hydrogen gas, iron in combination with hydrochloric acid, or tin (II) chloride in combination with hydrochloric acid. These reactions are typically performed in a protic solvent such as water, methyl alcohol, ethyl alcohol or a mixture thereof, and at temperatures ranging from ambient to 100 °C, preferably 40-85 °C. For example, compound 397 (Scheme XVI) is allowed to react with palladium on carbon in combination with hydrogen gas in ethyl alcohol at ambient temperature to afford compound 399.

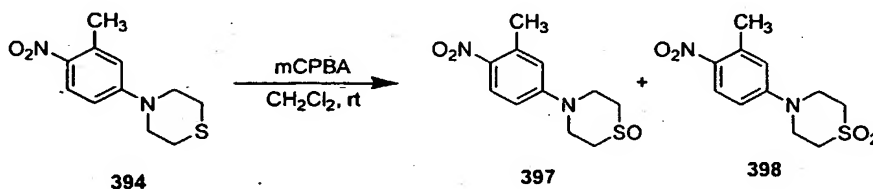


Scheme XVI



Compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8} alkyl, C_{1-8} alkoxy, nitro, nitrile, trifluoromethyl, and R_{17} is a heterocycle substituted with $-SO_2$, or $-S(O)$, can be prepared from compounds of formula XVI in which R_{17} is a heterocycle substituted with $-S$, by reaction with an agent capable of oxidizing a sulfide to a sulfoxide or a sulfone. Among the agents capable of affecting this transformation are meta-chloroperbenzoic acid (mCPBA), hydrogen peroxide, or oxone. These reactions are typically performed in solvents such as water, THF, acetonitrile, dichloromethane, methyl alcohol, ethyl alcohol, or a mixture thereof and at temperatures from 0 °C to 100 °C. For example, compound 394 (Scheme XVII) is allowed to react with MCPBA in chloroform at room temperature to provide both the sulfoxide 397 and the sulfone 398.

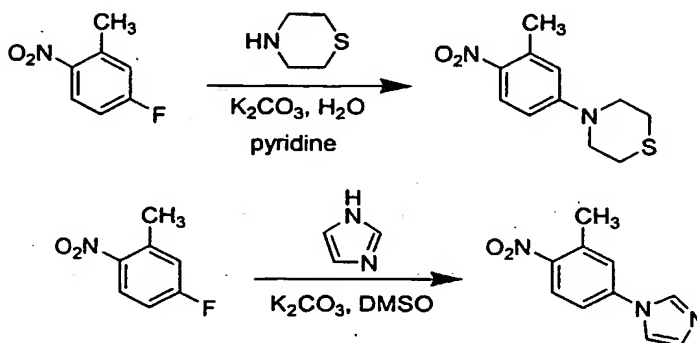
Scheme XVII



Compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8} alkyl, C_{1-8} alkoxy, nitro, nitrile, trifluoromethyl, and R_{17} is a heterocycle substituted with $-S$, or $-O$ can be prepared from compounds of formula XVI, in which R_{17} is or contains a suitable leaving group, such as a halide, preferably fluorine, chlorine, or bromine, by reaction with heterocyclic compounds capable of displacing the leaving group. Among the heterocycles that can affect this transformation are imidazole, 1,2,3-triazole, 1,2,4-triazole, morpholine, thiomorpholine, N-methylpiperazine, piperazine, and piperidine. These reactions are typically performed in an aprotic solvent such as dioxane, THF, dimethylsulfoxide or pyridine, and in the presence of a base such as triethylamine, or more preferably sodium or potassium carbonate, and at temperatures from 0 °C to 150 °C, preferably 50-100 °C. Two such examples are shown below in Scheme XIX. In the first example, 5-fluoro-2-nitrotoluene is allowed to react with thiomorpholine in pyridine and water and in the presence of potassium carbonate to afford compound X. In the second example, 5-fluoro-

2-nitrotoluene is allowed to react with imidazole in dimethylsulfoxide, in the presence of potassium carbonate, at 70 °C to provide compound 394.

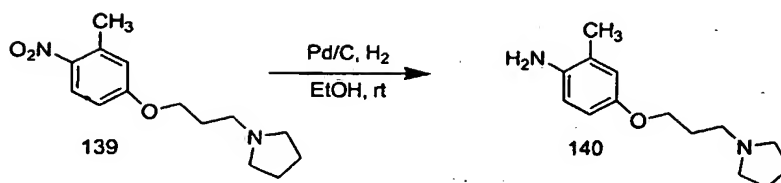
Scheme XIX



The desired heterocycles, such as those used in the schemes above, are either commercially available or can be prepared using literature methods familiar to those skilled in the art.

Compounds of formula XV, in which R_{14} is hydrogen, R_{15} is hydrogen, halogen, C_{1-8} -alkyl, C_{1-8} -alkoxy, nitro, nitrile, or trifluoromethyl, and R_{16} is $-OR_8$, wherein R_8 is C_{1-8} -alkyl, optionally substituted with C_{1-8} -alkoxide, alkylamine, $-SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, or heterocycle can be prepared from compounds of formula XVI in which R_{15} is hydrogen, halogen, C_{1-8} -alkyl, C_{1-8} -alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-OR_8$, by reaction with agents or a combination of agents which are capable of selectively reducing the nitro group to an amino group. Among the agents capable of affecting this transformation are palladium on carbon in combination with hydrogen gas, Raney nickel in combination with hydrogen gas, iron in combination with hydrochloric acid, or tin (II) chloride in combination with hydrochloric acid. These reactions are typically performed in a protic solvent such as water, methyl alcohol, ethyl alcohol or a mixture thereof, and at temperatures ranging from ambient to 100 °C, preferably 40-85 °C. For example, compound 139 (Scheme XX) is allowed to react with palladium on carbon in ethyl alcohol and in the presence of pressurized hydrogen gas to afford amine 140.

Scheme XX



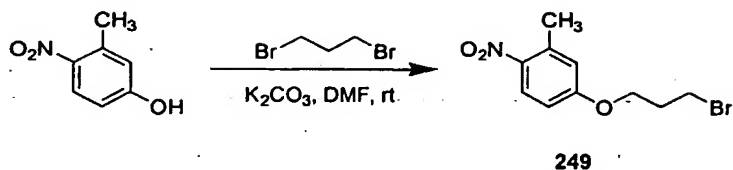
Compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8} alkyl, C_{1-8} alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-OR_8$, wherein R_8 is C_{1-8} alkyl, optionally substituted with C_{1-8} alkoxide, alkylamine, $-SO_2NR_6R_7$, wherein R_6 and R_7 are as

- 5 hereinbefore defined, or heterocycle can be prepared from compounds of formula XVI, in which R_{17} is hydroxy, by reaction with compounds of formula XVII in which R_{18} is C_{1-8} alkyl optionally substituted with C_{1-8} alkoxide, $-SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, or heterocycle, and R_{19} is a leaving group, preferably bromine or chlorine. These reactions are usually conducted in an aprotic solvent such as DMF, N-methylpyrrolidine, acetonitrile, or pyridine. In addition, the presence of a base such as triethylamine, or more preferably sodium or potassium carbonate is usually required. For example, 4-nitro-3-methylphenol (Scheme XXI) is allowed to react with 1,3-
- 10 dibromopropane in DMF and in the presence of potassium carbonate to afford compound 249.

$R_{19}-R_{18}$

XVII

Scheme XXI

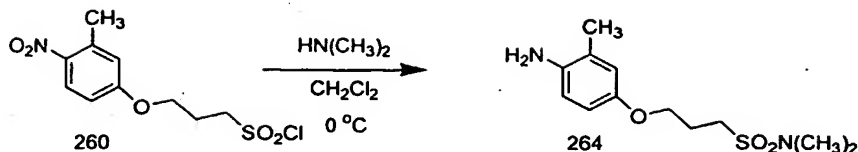


Compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8} alkyl, C_{1-8} alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-OR_8$, wherein R_8 is C_{1-8} alkyl substituted with $-SO_2NR_6R_7$, can be prepared from compounds of formula XVI, in which R_8 is C_{1-8} alkyl substituted with $-SO_2Cl$, by reaction with ammonia or an appropriate amine. These reactions are typically performed in aprotic solvents such as acetonitrile, or more preferably dichloromethane or chloroform. For example, sulfonyl chloride 260 (Scheme XXII) is allowed to react with dimethylamine in dichloromethane at 0°C to provide

20 sulfonamide 264.

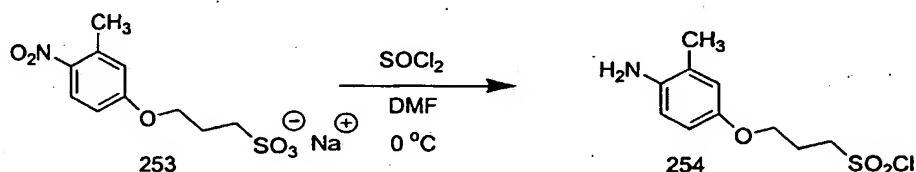
25

Scheme XXII



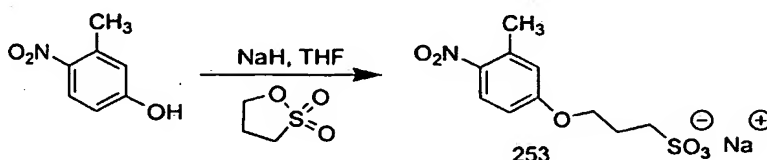
Compounds of formula XVI in which R_{15} is hydrogen, halogen, C_{1-8} alkyl, C_{1-8} alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-\text{OR}_8$, wherein R_8 is C_{1-8} alkyl substituted with $-\text{SO}_2\text{Cl}$, can be prepared from compounds of formula XVI in which R_{17} is $-\text{OR}_8$ and R_8 is C_{1-8} alkyl substituted with $-\text{SO}_3\text{H}$ or a salt thereof, by reaction with an agent capable of converting a sulfonic acid or a salt thereof to a sulfonyl chloride. Among the agents capable of affecting this transformation are POCl_3 , or more preferably thionyl chloride. These reactions are typically performed in an aprotic solvent such as dichloromethane, chloroform, or DMF. For example, compound 253 (Scheme XXIII) is allowed to react with thionyl chloride in DMF at 0°C to afford sulfonyl chloride 254.

Scheme XXIII



Compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8} alkyl, C_{1-8} alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-\text{OR}_8$, wherein R_8 is C_{1-8} alkyl substituted with $-\text{SO}_3\text{H}$ or a salt thereof, can be prepared from compounds of formula XVI, in which R_{17} is $-\text{OR}_8$, wherein R_8 is hydrogen, by reaction with a cyclic sulfonate ester, more commonly known as a sultone. These reactions are conducted in an aprotic solvent, such as DMF, acetonitrile, acetone, or more preferably THF and in the presence of a base such as potassium carbonate, or more preferably sodium hydride. For example, 3-methyl-4-nitrophenol (Scheme XXIV) is allowed to react with 1,3-propane sultone in THF and in the presence of sodium hydride to afford sulfonic acid salt 253.

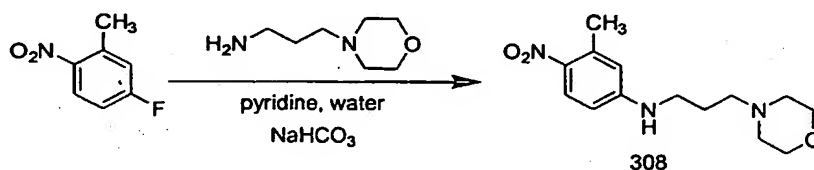
Scheme XXIV



The desired sultones, such as 1,3-propane sultone, are either commercially available or can be prepared by literature methods familiar to those skilled in the art.

Compounds of formula XVI, wherein R_{15} is hydrogen, halogen, C_{1-8} alkyl, C_{1-8} alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-NR_6R_7$, can be prepared from compounds of formula XVI, in which R_{17} is a suitable leaving group such as a halide, preferably chlorine or fluorine, by reaction with an appropriate amine. These reactions are conducted in solvents such as DMF, acetonitrile, dioxane, water, pyridine, or a mixture thereof, and in the presence of a base such as sodium or potassium carbonate, or more preferably sodium bicarbonate. For example, 5-fluoro-2-nitrotoluene (Scheme XXV) is allowed to react with 4-(3-aminopropyl)morpholine in pyridine and water and in the presence of sodium bicarbonate to provide compound 308.

Scheme XXV

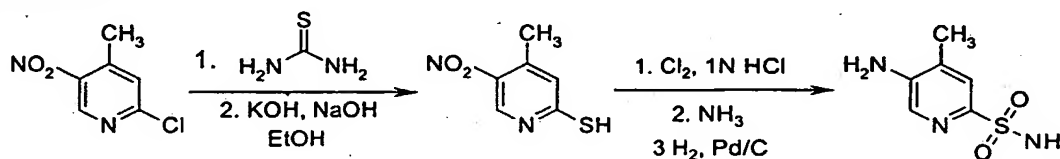


The desired amines of formula HNR_6R_7 are either commercially available or can be prepared using literature methods known in the art.

Compounds of formula V, in which R_3 is hydrogen and R_4 is an aromatic heterocycle, are either commercially available or can be prepared using literature methods familiar to those skilled in the art.

Compounds of formula (V) in which R_3 is hydrogen and R_4 is heterocycle, pyridine for example, substituted with $-SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, can be prepared by the methods shown below or by methods known to those skilled in the art. For example, 5-amino-4-methyl-2-pyridinesulfonamide can be prepared from 2-chloro-4-methyl-5-nitropyridine as shown in scheme XXVI. Commercially available 2-chloro-4-methyl-5-nitropyridine is allowed to react with an agent capable of displacing the 2-chloro group with a sulfur atom to provide 4-methyl-5-nitro-2-pyridinethiol, for example, thiourea. These reactions are typically performed in a polar, protic solvent, acetic acid, for example and in the presence of a base, potassium and sodium hydroxide for example, and at temperatures from 20 °C to 150 °C. The resulting thiol is then allowed to react with a reagent capable of oxidizing the thiol to the sulfonic acid derivative, for example hydrogen

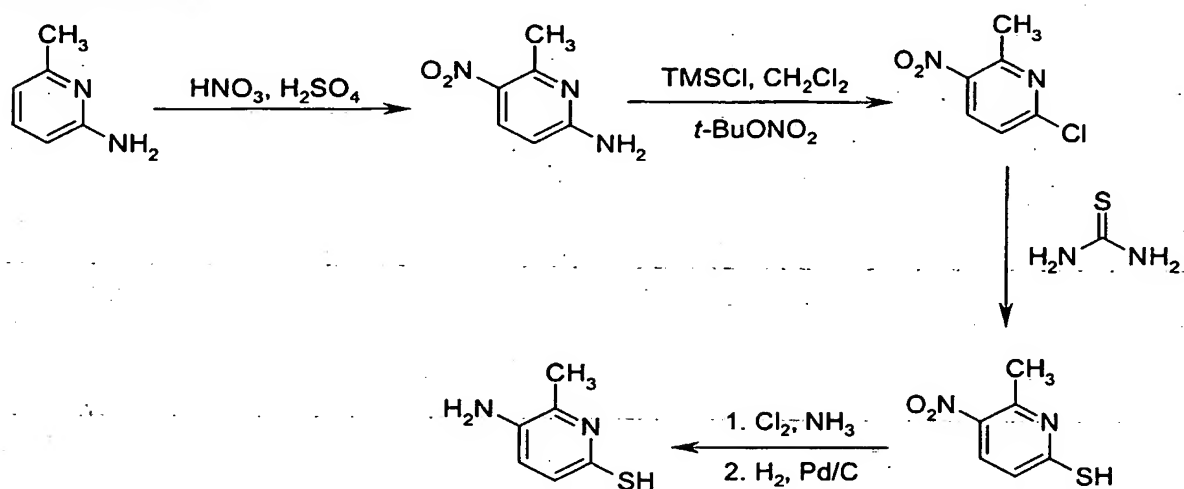
peroxide, oxone or chlorine gas. The oxidation can be advantageously performed using chlorine gas as the oxidizing agent in an acidic solvent, 1N hydrochloric acid for example, with the concomitant formation of the corresponding, desired sulfonyl chloride. The resulting sulfonyl chloride is then allowed to react with an agent capable of converting it to the corresponding sulfonamide, ammonia gas or a solution of ammonia in an appropriate solvent such as dichloromethane, to provide 4-methyl-5-nitro-2-pyridinesulfonamide. The nitro group can then be reduced using methods known to those skilled in the art, palladium on carbon in the presence of hydrogen gas as the reducing agent for example, to produce the desired 5-amino-4-methyl-2-pyridinesulfonamide. The reduction reactions are typically performed in a polar, protic solvent, methanol for example, and at temperatures from 20 °C to 100 °C, preferably at ambient temperature.

Scheme XXVI

Alternatively, compounds of formula (V), in which R_3 is hydrogen and R_4 is heterocycle, pyridine for example, substituted with $-\text{SO}_2\text{NR}_6\text{R}_7$, wherein R_6 and R_7 are as hereinbefore defined, can be prepared by the methods shown below or by methods known to those skilled in the art. For example, 5-amino-6-methyl-2-pyridinesulfonamide can be prepared as shown in scheme XXVII. Commercially available 2-amino-5-methylpyridine is allowed to react with an agent capable of nitrating the pyridine ring, for example a mixture of nitric and sulfuric acids. These reactions are typically performed in concentrated sulfuric acid as solvent, and at temperatures from -10°C to 25°C , preferably at 0°C , to produce the desired 5-amino-2-methyl-3-nitropyridine. The amino group is then allowed to react with a combination of agents capable of converting the amino group to a chlorine substituent. For example, 5-amino-2-methyl-3-nitropyridine was allowed to react with tert-butyl nitrite, to produce the corresponding diazonium salt, followed by reaction with trimethylsilyl chloride in an aprotic solvent, dichloromethane for example, to afford 5-chloro-2-methyl-3-nitropyridine. The chloro group is then allowed to react with an agent capable of effecting a substitution on the pyridine ring to produce the corresponding thiol derivative. For example, 5-chloro-2-methyl-3-nitropyridine was allowed to react with thiourea in a mixture of acetic acid, potassium hydroxide and sodium hydroxide to afford

the desired 6-methyl-5-nitro-2-pyridinethiol. The resulting thiol is then allowed to react with a reagent capable of oxidizing the thiol to the sulfonic acid derivative, for example hydrogen peroxide, oxone or chlorine gas. The oxidation can be advantageously performed using chlorine gas as the oxidizing agent in an acidic solvent, 1N hydrochloric acid for example, with the concomitant formation of the corresponding, desired sulfonyl chloride. The resulting sulfonyl chloride is then allowed to react with an agent capable of converting it to the corresponding sulfonamide, ammonia gas or a solution of ammonia in an appropriate solvent such as dichloromethane, to provide 6-methyl-5-nitro-2-pyridinesulfonamide. The nitro group can then be reduced using methods known to those skilled in the art, palladium on carbon in the presence of hydrogen gas as the reducing agent for example, to produce the desired 5-amino-6-methyl-2-pyridinesulfonamide. The reduction reactions are typically performed in a polar, protic solvent, methanol for example, and at temperatures from 20 °C to 100 °C, preferably at ambient temperature.

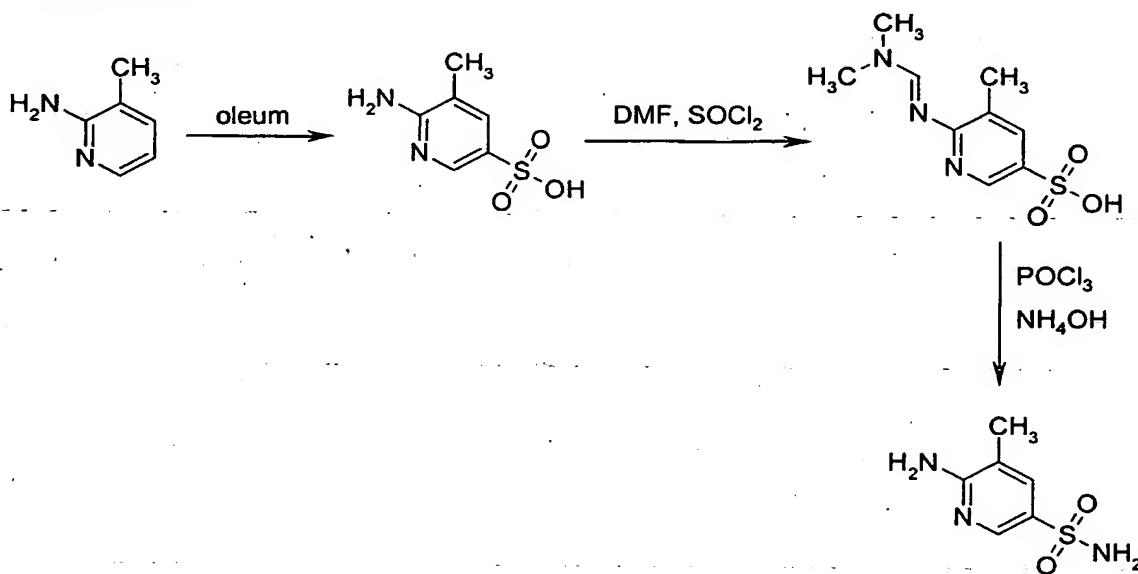
Scheme XXVII



Alternatively, compounds of formula (V) in which R_3 is hydrogen and R_4 is heterocycle, pyridine for example, substituted with $-\text{SO}_2\text{NR}_6\text{R}_7$, wherein R_6 and R_7 are as hereinbefore defined, can be prepared by the methods shown below or by methods known to those skilled in the art. For example, 6-amino-5-methyl-3-pyridinesulfonamide can be prepared as shown in scheme XXVIII. Commercially available 2-amino-3-methylpyridine is allowed to react with an agent capable of sulfonylating the pyridine ring, for example oleum. These reactions are typically performed in a mixture of 20% $\text{SO}_3/\text{H}_2\text{SO}_4$, at

temperatures ranging from 75 °C to 200 °C, preferably 160°C, to produce 6-amino-5-methyl-3-pyridinesulfonic acid. The amino group is then allowed to react with a combination of agents capable of effecting protection of the amino group from oxidation in subsequent steps. For example, 6-amino-5-methyl-3-pyridinesulfonic acid was allowed to react with a mixture of N,N-dimethylformamide (DMF) and thionyl chloride, so-called Vilsmier reagents, to produce the desired 6-[(dimethylamino)methylidene]amino-5-methyl-3-pyridinesulfonic acid intermediate. This compound is then allowed to react with a combination of agents capable of converting the sulfonic acid to the corresponding sulfonyl chloride, followed by reaction with an agent capable of converting the sulfonyl chloride to the corresponding sulfonamide derivative. For example, desired 6-[(dimethylamino)methylidene]amino-5-methyl-3-pyridinesulfonic acid is allowed to react with phosphorous oxychloride to produce the intermediate sulfonyl chloride, followed by reaction with ammonium hydroxide, to afford the desired 6-amino-5-methyl-3-pyridinesulfonamide.

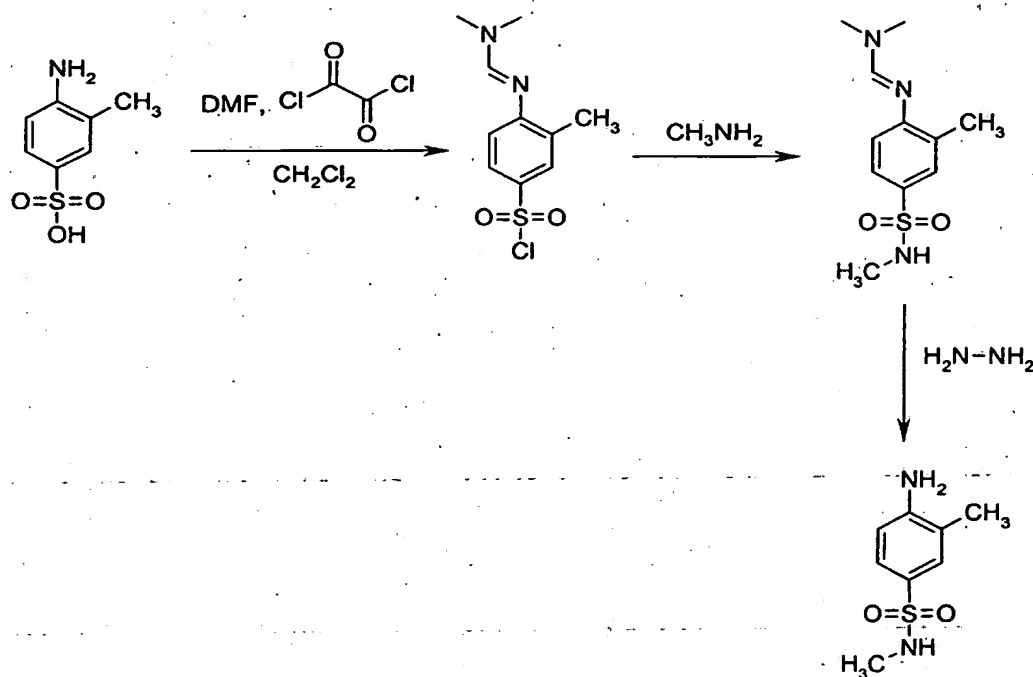
Scheme XXVIII



Compounds of formula (XV) wherein R₁₄ is hydrogen, R₁₅ is hydrogen halogen, C₁₋₈alkyl, C₁₋₈alkoxy, nitro, nitrile, trifluoromethyl, and R₁₆ is -SO₂NR₆R₇, wherein R₆ and R₇ are as hereinbefore defined, can be prepared by methods known in the art or by the method shown in Scheme XXIX. For example, 4-amino-N,3-dimethylbenzenesulfonamide can be prepared from commercially available 4-amino-3-methylbenzenesulfonic acid by

reaction with a combination of reagents capable of effecting protection of the amino group from oxidation in later chemical steps. For example, 4-amino-3-methylbenzenesulfonic acid was allowed to react with N,N-dimethylformamide (DMF) and oxalyl chloride in dichloromethane to effect the concomitant protection of the amino group as the corresponding amidine as well as converting the sulfonic acid to the desired sulfonyl chloride. The sulfonyl chloride was then allowed to react with an amine, methyl amine for example, to produce 4-[(dimethylamino)methylidene]amino-N,3-dimethylbenzenesulfonamide. The amidine-protecting group was then removed using hydrazine hydrochloride.

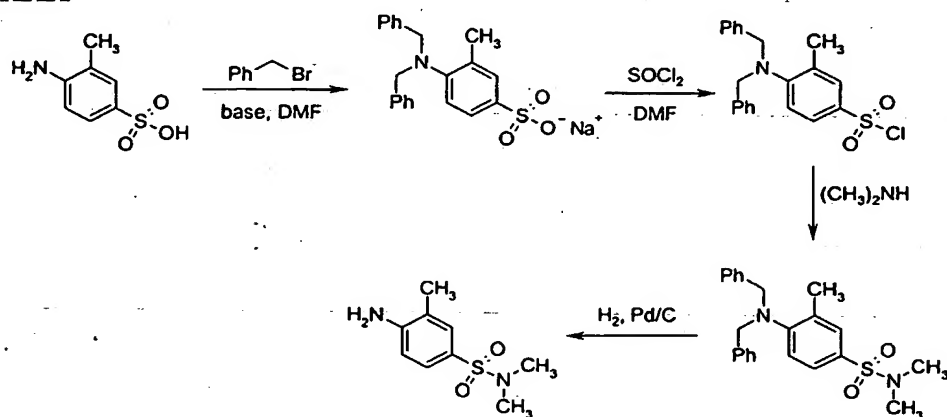
10 **Scheme XXIX**



Alternatively, compounds of formula (XV), wherein R₁₄ is hydrogen, R₁₅ is hydrogen halogen, C₁₋₈alkyl, C₁₋₈alkoxy, nitro, nitrile, trifluoromethyl, and R₁₆ is -SO₂NR₆R₇, wherein R₆ and R₇ are as hereinbefore defined, can be prepared by methods known in the art or by the method shown in Scheme XXX. For example, 4-amino-N,N,3-trimethylbenzenesulfonamide can be prepared by methods known in the art or as shown in Scheme XXX. Commercially available 4-amino-3-methylbenzenesulfonic acid is allowed to react with an agent capable of effecting protection of the amino group from oxidation in further synthetic steps. For example, 4-amino-3-methylbenzenesulfonic acid was allowed

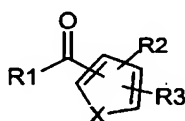
to react with benzyl bromide in the presence of a base, sodium or potassium carbonate for example, to afford sodium 4-(dibenzylamino)-3-methylbenzenesulfonate. These reactions are typically performed in a polar, aprotic solvent, N,N-dimethylformamide for example, at temperature ranges from 25 °C to 125 °C, preferably 75-100 °C. The sodium salt is then allowed to react with an agent capable of converting the salt to the corresponding sulfonyl chloride. For example, sodium 4-(dibenzylamino)-3-methylbenzenesulfonate was allowed to react with thionyl chloride in N,N-dimethylformamide (DMF) to afford the desired 4-(dibenzylamino)-3-methylbenzenesulfonyl chloride. These reactions are typically performed in an aprotic solvent, dichloromethane for example, and at temperatures from 0 °C to 75 °C, preferably 0 °C. The sulfonyl chloride is then allowed to react with an appropriate amine to afford the desired sulfonamide. For example, 4-(dibenzylamino)-3-methylbenzenesulfonyl chloride was allowed to react with dimethylamine to afford the desired 4-(dibenzylamino)-N,N,3-trimethylbenzenesulfonamide. The sulfonamide is then allowed to react with a combination of agent capable of effecting the deprotection of the amine to produce the desired aniline derivative. For example, desired 4-(dibenzylamino)-N,N,3-trimethylbenzenesulfonamide was allowed to react with hydrogen gas in the presence of a palladium on carbon catalyst to effect cleavage of the benzyl protecting groups and afford the desired 4-amino-N,N,3-trimethylbenzenesulfonamide.

Scheme XXX

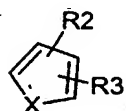


Compounds of formula XVIII where R₂ is either a hydroxy or methoxy group and R₁ and R₃ are as hereinbefore defined, and X is a heteroatom, preferably oxygen or sulfur, can be prepared from compounds of formula XIX with compounds of formula X where R₁ is hereinbefore defined and R₁₀ is a halogen, preferably chlorine, with the stipulation that

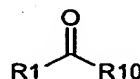
R_1 and R_3 are chemically compatible with the reaction conditions and that R_2 , R_3 and R_1CO are regiochemically compatible in such reactions. These reactions, typically called Friedel-Craft acylations, are performed according to processes previously described (see, for example, Scheme X). For example, 3-methoxythiophene (Scheme XXXI) is allowed to react with benzoyl chloride in refluxing dichloromethane in the presence of aluminum chloride to afford ketone 664.



XVIII

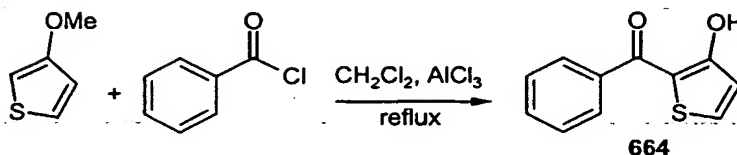


XIX



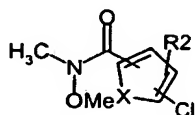
X

Scheme XXXI



Compounds of formula XVIII where R_1 and R_3 are as hereinbefore defined and R_2 is methoxy and X is a heteroatom, preferably sulfur or oxygen, can be prepared from the reaction of compounds of formula XX in which R_2 and R_3 are as hereinbefore defined with compounds of XIII in which R_1 is as hereinbefore defined, and R_{11} is a halogen, preferably bromine or iodine, with the stipulation that R_1 and R_5 are chemically compatible with subsequent chemical steps and that the N,O-dimethylhydroxyacetamide, R_2 and R_3 groups

are regiochemically compatible in such a reaction. Typically, conditions for such reactions are similar to those described for the synthesis of compounds of formula XII.



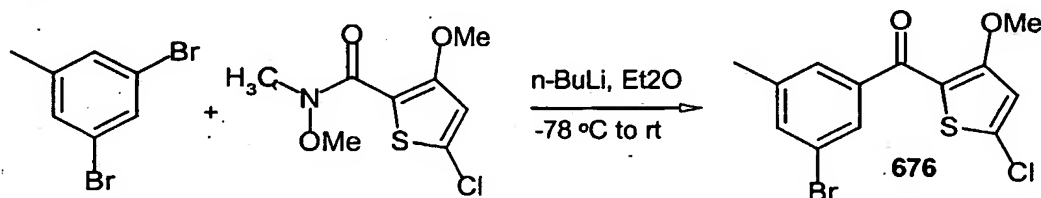
XX



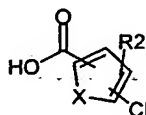
XIII

For example, 3,5-dibromotoluene in diethyl ether was treated with n-butyllithium at -78 °C. After 15 minutes at -78 °C, the resulting lithium species is allowed to react with 675 to afford the desired ketone 676 (see Scheme XXXIII).

10 Scheme XXXIII



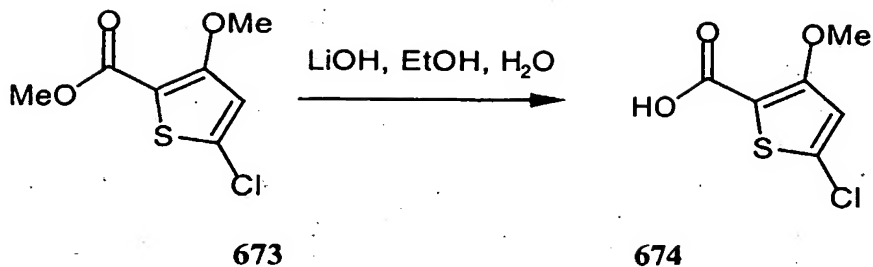
Finally, compounds of formula XX can be prepared from compounds of formula XXI where R₂ and R₃ are as hereinbefore defined using procedures previously described for the synthesis of compounds of formula X (See Scheme VII).



XXI

Compounds of formula XXI can, in turn, be prepared according to procedures described in the literature. See for example *Synthesis*, 1984, 847 for the synthesis of 673 which after hydrolysis provided compound 674 (Scheme XXXIV).

Scheme XXXIV



- 5 A further object of the present invention features intermediates 7, 32, 33, 36, 38, 44, 45, 49, 51, 52, 61, 65, 66, 71, 75, 76, 111, 112, 115, 118, 119, 128, 129, 171, 172, 191, 192, 199, 200, 206, 207, 224, 225, 232, 233, 235, 236, 246, 247, 253, 254, 255, 256, 259, 260, 261, 262, 264, 265, 267, 268, 288, 289, 290, 409, 412, 428, 430, 431, 433, 477, 490, 495, 496, 507, 511, 514, 515, 518, 519, 522, 523, 526, 527, 529, 530, 532, 533, 537, 538, 540, 10 541, 543, 544, 546, 553, 556, 558, 559, 561, 562, 567, 568, 572, 573, 576, 577, 582, 584, 585, 588, 589, 595, 602, 603, 608, 611, 612, 616, 620, 621, 638, 639, 648, 653, 661, 662, 671, 676, 677 useful in the manufacture of the compounds of the present invention.

15 The compounds according to the invention, also referred to herein as the active ingredient, may be administered for therapy by any suitable route including oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and intravitreal). It will be appreciated that the preferred route will vary with the condition and age of the recipient, the nature of the infection and the chosen active ingredient.

20

In general a suitable dose for each of the above-mentioned conditions will be in the range of 0.01 to 250 mg per kilogram body weight of the recipient (e.g. a human) per day, preferably in the range of 0.1 to 100 mg per kilogram body weight per day and most preferably in the range 0.5 to 30 mg per kilogram body weight per day and particularly in 25 the range 1.0 to 20 mg per kilogram body weight per day. Unless otherwise indicated, all weights of active ingredient are calculated as the parent compound of formula (I); for salts or esters thereof, the weights would be increased proportionally. The desired dose may be presented as one, two, three, four, five, six or more sub-doses administered at appropriate

intervals throughout the day. In some cases the desired dose may be given on alternative days. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1000 mg or 50 to 500 mg, preferably 20 to 500 mg, and most preferably 100 to 400 mg of active ingredient per unit dosage form.

5

While it is possible for the active ingredient to be administered alone it is preferable to present it as a pharmaceutical formulation. The formulations of the present invention comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof and optionally other therapeutic agents. Each carrier must be

10 "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

15

Formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and intravitreal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier which constitutes one or more accessory ingredients. In general, the

20 formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

25

The present invention further includes a pharmaceutical formulation as hereinbefore defined wherein a compound of formula (I) or a pharmaceutically acceptable derivative thereof and at least one further therapeutic agent are presented separately from one another as a kit of parts.

30

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3)

dispersed in a polymer. A suitable concentration of the active compound is about 1% to 25%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport or iontophoresis as generally described in *Pharmaceutical Research* 3 (6), 318 (1986).

5 Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a
10 water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable
15 machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered
20 compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other
25 than the stomach.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and
30 glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

Formulations suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or daily subdose of the active ingredients, as hereinbefore recited, or an appropriate fraction thereof.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral

administration may include such further agents as sweeteners, thickeners and flavoring agents.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way. "Active ingredient" denotes a compound according to the invention or multiples thereof or a physiologically functional derivative of any of the aforementioned compounds.

General Procedures:

General procedure I: Friedel-Crafts reaction of acid chlorides with 4-chloroanisole

Into a round-bottom flask equipped with a stir bar, a reflux condenser, and nitrogen on demand, were placed 4-chloroanisole (1-1.25 mmol/mmol of acid chloride), aluminum chloride (AlCl_3 , 1-1.75 mmol/mmol of acid chloride) and CH_2Cl_2 . To the resulting mixture was added the appropriate acid chloride at rt. When the addition was complete, the orange mixture was heated to reflux and was allowed to stir for 2-24 h. The mixture was allowed to cool to rt and was carefully poured onto ice water, giving a two-phase mixture which was stirred at rt for 30 min to 2 h. It was then poured into a separatory funnel containing water. The organic layer was collected, washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure. See specific examples for details regarding additional purification.

General procedure II: Alkylation of phenols with ethyl bromoacetate

Into a round-bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand were placed the appropriate phenol, potassium carbonate (2-10 mmol/mmol of phenol), ethyl bromoacetate (1-1.5 mmol/mmol of phenol) and acetone (1-10 mL/mmol of phenol). The resulting mixture was heated to reflux for 1-20 h, after which time it was allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to leave an oil. See specific examples for details regarding additional purification.

General procedure III: Saponification of ethyl esters to the carboxylic acids

A round-bottom flask was equipped with a stir bar, nitrogen on demand and was flushed with nitrogen. To the flask were added tetrahydrofuran (THF, 1-5 mL/mmol of ester), ethyl alcohol (EtOH, 1-5 mL/mmol of ester), water (1-5 mL/mmol of ester) and lithium hydroxide monohydrate (1-5 mmol/mmol of ester). The resulting suspension was stirred vigorously and the ester was added in one portion. The mixture was allowed to stir at rt for 1-20 h, after which time the pH was adjusted to approximately pH 5 by the slow addition of 1 N aqueous hydrochloric acid. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to leave a white solid. See specific examples to determine if further purification of the product was required.

General procedure IV: Coupling of the acid to aromatic amines using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC)

A round-bottom flask was equipped with a stir bar, nitrogen on demand and was flushed with nitrogen. To the flask were added the appropriate carboxylic acid, N,N-dimethylformamide (DMF, 5-20 mL/mmol acid), 1-hydroxybenztriazole (HOBt, 1-2 mmol/mmol acid), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC, 1-5 mmol/mmol acid), and the appropriate aromatic amine (1-2 mmol/mmol acid). In some cases, triethylamine (Et_3N , 2-5 mmol/mmol of acid) was used. The resulting mixture was allowed to stir at rt for 2-24 h, after which time it was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure. See specific examples for details regarding further purification of the products.

General Procedure V: Synthesis of acid chlorides from carboxylic acids using oxalyl chloride

Into a round-bottom flask were placed the appropriate carboxylic acid, methylene chloride (CH_2Cl_2 , 1-10 mL/mmol acid), and N,N-dimethylformamide (1-10 drops). The mixture was cooled to 0 °C and oxalyl chloride (1-2 mmol/mmol acid) was added dropwise, after

which time the mixture was allowed to warm to rt and stir for 1-24 h. The solvents were then removed under reduced pressure and the remaining residue was dried in vacuo. In most cases, the acid chlorides were used immediately used in subsequent reactions with no further purification.

General procedure VI: Coupling of acid chlorides to aromatic amines using sodium bicarbonate

- 10 Into a round-bottom flask were placed the appropriate aromatic amine, acetone (1-10 mL/mmol amine), sodium bicarbonate (2-10 mmol/mmol amine), and water (0.25-10 mL). The acid chloride was added as a solution in acetone (1-10 mL/mmol of acid chloride) in a dropwise manner and the reaction mixture was allowed to stir at rt for 1-24 h. When judged to be complete, the mixture was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure. See specific examples for details regarding further purification of the products.

General procedure VII: Synthesis of Weinreb amides from acid chlorides using N,O-dimethylhydroxylamine hydrochloride

- 20 Into a round bottom flask equipped with a stir bar and nitrogen on demand were placed the N,O-dimethylhydroxylamine (1-2 mmol/mmol acid chloride) and chloroform (CHCl_3 , 1-10 mL/mmol acid chloride). The mixture was cooled to 0°C and triethylamine (Et_3N , 1-5 mmol/mmol acid chloride) was added in one portion. The acid chloride was added and the reaction mixture was allowed to stir at 0°C for 0.5-5 h, after which time was poured into a separatory funnel containing chloroform and water. The organics were collected, washed with water and brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure. See specific examples to determine if further purification of the product was required.

General procedure VIII: Halogen-metal exchange of 2-bromo-4-chloroanisole, followed by addition of Weinreb amides

Into a round-bottom flask equipped with a stir bar, nitrogen on demand, and an addition funnel, were added 2-bromo-4-chloroanisole (1 mmol/mmol of amide) and diethyl ether (1-10 mL/mmol of anisole) and the mixture was cooled to -78°C by means of a dry ice/acetone bath. N-Butyl lithium (1-2 mmol/mmol of anisole of a 2.5M soln. in hexanes) was added dropwise, followed by addition of the Weinreb amide. The reaction was allowed to stir at -78°C for 0.5h-1h, at which time the reaction was allowed to warm to rt. When judged to be complete, the reaction was poured into a separatory funnel containing ether and water. The organics were collected, washed with water, dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. See specific examples to determine if further purification was required.

General procedure IX: Deprotection of anisole derivatives using boron tribromide

To a round-bottom flask equipped with a stir bar, nitrogen on demand, and an addition funnel was added the appropriate anisole derivative and methylene chloride (CH_2Cl_2 , 1-15 mL/mmol of anisole). The mixture was cooled to -78°C and boron tribromide was added dropwise at -78°C . The resulting mixture was allowed to stir at -78°C for 30-120 minutes, after which time it was allowed to warm to rt and stir for an additional 15-120 minutes. When judged to be complete, the reaction was poured over ice and extracted with CH_2Cl_2 . The organics were collected, washed with water, dried over MgSO_4 , filtered, and the solvents were removed. See specific examples to determine if further purification was required.

General Procedure X: The appropriate acid chloride in acetonitrile was added dropwise via an addition funnel to a stirred solution of triethylamine (0-2.5mmol/mmol acid chloride), acetonitrile (1-20 ml/mmol acid chloride), and the appropriate aniline (0.5-2.5 mmol/mmol acid chloride). The reaction was refluxed for 0-12 h. The heat was removed and the reaction mixture was stirred for 12-336 h. The mixture was concentrated, dissolved, and washed with water. The resulting organics were dried over MgSO_4 and concentrated in vacuo and purified as described in the individual cases.

General Procedure XI. An amine (1-2.5 mmol/mmol benzene) was added dropwise via an addition funnel to a stirred suspension of a para-nitro halogenated benzene or toluene in

pyridine (20-40 mmol/mmol benzene), sodium bicarbonate (1.5-4 mmol/mmol benzene), and water (0.2-5 mL/mmol benzene). The resulting suspension was refluxed (150 °C) for 1-7 days. The mixture was filtered and acetone (10-200 mL/mmol benzene) was added to the filtrate and brought to reflux. Water was added to the cloud point and the solution was cooled to rt. The precipitate was filtered and the resulting solid was washed with water and ether to afford the substituted product.

General Procedure XII. The appropriate nitro-benzene was added to a suspension of palladium on carbon (0.1-0.8 mmol /mmol benzene, 10% w/w), ethanol, THF, and methanol and the reaction vessel was evacuated and charged with nitrogen several times. After evacuating the reaction vessel under reduced pressure, it was charged with hydrogen (14-100 psi). The resulting suspension was stirred at rt for 0-72 h, filtered through a celite pad, and concentrated in vacuo to afford the appropriate aniline.

General procedure XIII. Into a round-bottom flask equipped with a stir bar, cooling bath, and nitrogen on demand were placed the appropriate carboxylic acid, hexachloroacetone (HCA, 0.5 mmol/mmol acid), and THF (1-10 mL/mmol acid) and the mixture was cooled -78 °C. Triphenylphosphine (PPh₃, 1 mmol/mmol acid) in THF (1-10 mL/mmol acid) was added to the mixture and stirred for 5-120 min. The appropriate aniline (1 mmol/mmol acid) in THF (1-10 mL/mmol acid) and pyridine (5-20 mmol/mmol acid) were added dropwise and the mixture was stirred -78 °C for 5-60 min. The cooling bath was removed and the mixture was stirred at rt for 1h to 14 d. The reaction mixture was concentrated in vacuo and purified as described in the individual cases.

General procedure XIV. Thionyl chloride (1-100 mmol/mmol acid) was added to a solution of the appropriate carboxylic acid in methylene chloride (1-100 ml/mmol acid) and the resulting solution was refluxed for 1-12 h under nitrogen. The mixture was concentrated in vacuo and placed under nitrogen to afford the appropriate acid chloride.

General Procedure XV: Palladium-mediated cyanation of benzophenone derivatives

The appropriate bromobenzophenone was treated according to the procedures outlined by Anderson et al. in *J. Org. Chem.* 1998, 63, 8224-8228. Into a heat-dried flask, fitted with a reflux condenser, was placed the bromo- or trifluoromethylsulfonyl- benzophenone (1 eq),

tetrakis(triphenylphosphine) palladium (10-20%), copper iodide (2 eq relative to palladium), sodium cyanide (2 eq), and propionitrile (0.5-1.0 M in bromobenzophenone). The mixture was purged with N₂ for 30 min prior to use. The mixture was heated to 120 °C and stirred until TLC analysis showed complete disappearance of the starting material (1-16 h). The mixture was then cooled to rt, diluted with ethyl acetate, and filtered through silica gel, and the filtrate was concentrated in vacuo. The corresponding products were purified as described in each example..

General procedure XVI: Synthesis of *N*-[4-(aminosulfonyl)-2-methylphenyl]acetamide and *N*-[4-(alkyl and dialkyaminosulfonyl)-2-methylphenyl]acetamides

Sulfonyl chloride 464 (1-100 mmol) was added to a solution of the appropriate amine in pyridine (1-10 mL/mmol amine) and the resulting solution was stirred for 1-48 h under nitrogen. Water was added and the resulting mixture was extracted with methylene chloride and the organics were concentrated in vacuo. The resulting products were then purified by flash chromatography to afford the appropriate acetyl protected sulfonamide.

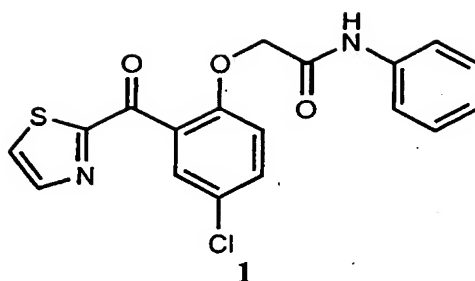
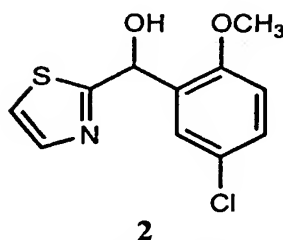
General procedure XVII: De-acetylation of *N*-[4-(aminosulfonyl)-2-methylphenyl]acetamide and *N*-[4-(alkyl and dialkyaminosulfonyl)-2-methylphenyl]acetamides

The appropriate sulfonamide (1-100 mmol) was added to a solution of ethanol (1-50 mL), water (0-5mL), and hydrochloric acid (1-28.9 M, 1-50 mL) in a large test tube. The mixture was then heated, with stirring, to 60 °C for 1-36 h. The mixture was allowed to cool to rt and concentrated in vacuo. The resulting products were dissolved in ethyl acetate and washed with saturated NaHCO₃, then purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford the desired aniline.

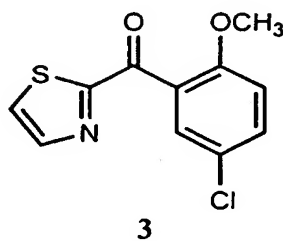
Examples:

Example 1:

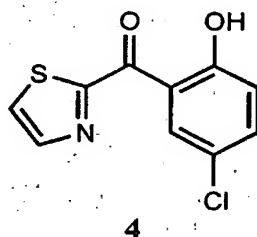
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**Step A:**

A solution of 2-Bromo-4-Chloroanisole (8.98 g, 40.54 mmol) in diethyl ether (65 mL) was cooled to -78°C and n-butyl lithium (26 mL of a 1.6 M solution in hexanes, 41.6 mmol) was added from a syringe. The resulting orange solution was allowed to stir at -78°C for 30 min, after which time 2-thiazolecarboxaldehyde (4.53 g, 40.04 mmol) was added neat, resulting in a purple solution. The mixture was allowed to stir at -78°C for 15 min, after which time water (50 mL) was added and the mixture was allowed to warm to RT. The mixture was poured into a separatory funnel containing ether and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to afford a white solid. The solid was washed with hexanes and was dried in vacuo; affording white needles (5.21 g, 51%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.70 (d, $J=4\text{ Hz}$, 1H), 7.38 (d, $J=4\text{ Hz}$, 1H), 7.28 (d, $J=4\text{ Hz}$, 1H), 7.23 (m, 1H), 6.83 (d, $J=8\text{ Hz}$, 1H), 6.23 (d, $J=8\text{ Hz}$, 1H), 3.99 (d, $J=8\text{ Hz}$, 1H), 3.83 (s, 3H).

Step B:

2 (5.21 g, 20.6 mmol), manganese dioxide (17.66 g, 203.1 mmol) and methylene chloride (CH_2Cl_2 , 75 mL) were combined under nitrogen and were allowed to stir at RT for 2.5 h. The mixture was filtered through a pad of celite, which was washed with several portions of CH_2Cl_2 , and the solvent was removed under reduced pressure to provide a tan solid (4.96 g, 95%) which was used in subsequent reactions without any further purification. ^1H NMR (CDCl_3 , 300 MHz) δ 8.06 (d, J = 3 Hz, 1H), 7.76 (d, J = 3 Hz, 1H), 7.63 (d, J = 3 Hz, 1H), 7.49 (dd, J = 9, 3 Hz, 1H), 7.00 (d, J = 9 Hz, 1H), 3.82 (s, 3H).

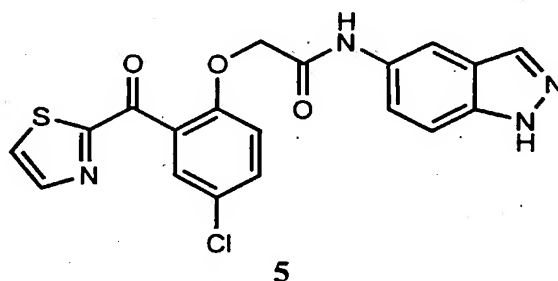
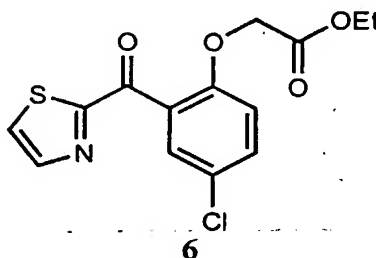
Step C:

3 (4.96 g, 19.6 mmol), in CH_2Cl_2 (60 mL) was cooled to -78°C and boron tribromide (100 mL of a 1.0 M solution in CH_2Cl_2 , 100 mmol) was added via syringe over 30 min. The resulting purple solution was allowed to stir at -78°C for 15 min, after which time it was allowed to slowly warm to RT. After 30 min at RT, the mixture was slowly poured over ice water and the resulting two-phase mixture was allowed to stir for 30 min. The mixture was then poured into a separatory funnel containing water and CH_2Cl_2 . The organic layer was collected and was washed with water, brine, dried over MgSO_4 , and the solvents were removed under reduced pressure. The product was isolated by flash chromatography using 7:3 hexane/ CH_2Cl_2 to provide a yellow solid (3.59 g, 76%). ^1H NMR (CDCl_3 , 300 MHz) δ 12.25 (s, 1H), 9.29 (d, J = 3 Hz, 1H), 8.19 (d, J = 3 Hz, 1H), 7.83 (d, J = 3 Hz, 1H), 7.53 (dd, J = 9, 3 Hz, 1H), 7.05 (d, J = 9 Hz, 1H).

Step D:

4 (0.12 g, 0.49 mmol), 2'-chloroacetanilide (0.09 g, 0.52 mmol), sodium carbonate (Na_2CO_3 , 0.54 g, 5.1 mmol), potassium iodide (0.47 g, 3.1 mmol) and acetone (8 mL) were combined under nitrogen and the resulting mixture was heated to reflux. After 18 h at reflux, the mixture was allowed to cool to RT and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with

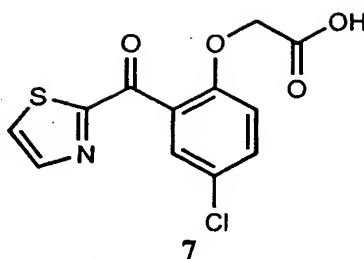
water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure, leaving orange oil. The product was isolated by flash chromatography using 4:1 hexane/ethyl acetate as eluant to provide 1 as a white solid (0.09 g, 49%). ^1H NMR (CDCl_3 , 300 MHz) δ 9.66 (s, 1H), 9.04 (d, $J = 3$ Hz, 1H), 7.93 (d, $J = 2.7$ Hz, 1H), 7.78 (d, $J = 3$ Hz, 1H), 7.72 (d, $J = 8$ Hz, 2H), 7.51 (dd, $J = 3$ Hz, 1H), 7.35 (m, 2H), 7.15 (m, 1H), 6.97 (d, $J = 9$ Hz, 1H), 4.67 (s, 2H).

Example 2:**Step A:**

Phenol 4 (2.31 g, 9.64 mmol), K_2CO_3 (6.95 g, 50.3 mmol), ethyl bromoacetate (1.1 mL, 1.7 g, 9.9 mmol) and acetone (150 mL) were used according to general procedure II. The product was used in the next reaction without any further purification. ^1H NMR (CDCl_3 , 300 MHz) δ 8.05 (d, $J = 3$ Hz, 1H), 7.76 (d, $J = 3$ Hz, 1H), 7.66 (d, $J = 3$ Hz, 1H), 7.48 (dd, $J = 9, 3$ Hz, 1H), 6.93 (d, $J = 9$ Hz, 1H), 4.61 (s, 2H), 4.21 (q, $J = 6$ Hz, 2H), 1.26 (t, $J = 6$ Hz, 3H).

Step B:

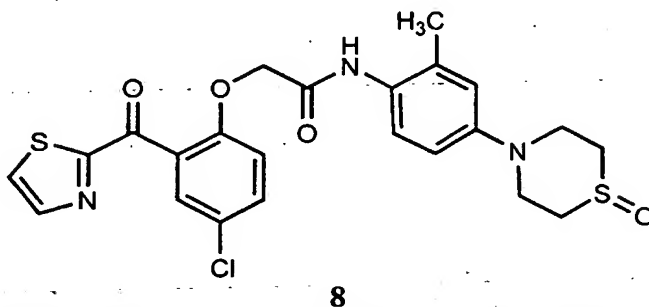
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Ester 6 (3.1 g, 9.6 mmol), THF (30 mL), water (10 mL), EtOH (10 mL) and LiOH (1.0 g, 23.8 mmol) were used according to general procedure III. The product was used in the next reaction without any further purification. ¹H NMR (DMSO-d₆, 300 MHz) δ 8.30 (d, J = 3 Hz, 1H), 8.15 (d, J = 3 Hz, 1H), 7.63 (d, J = 3 Hz, 1H), 7.57 (dd, J = 9, 3 Hz, 1H), 7.05 (d, J = 9 Hz, 1H), 4.45 (s, 2H).

Step C:

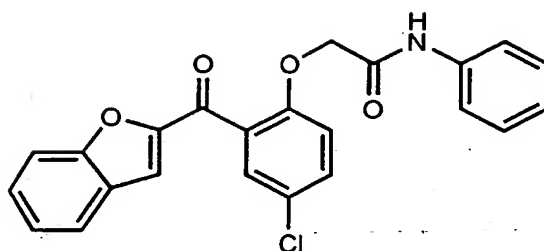
Carboxylic acid 7 (0.1 g, 0.33 mmol), HOBt (0.05 g, 0.4 mmol), EDAC (0.09 g, 0.46 mmol), Et₃N (0.1 mL, 0.07 g, 0.72 mmol), DMF (6 mL) and 5-aminoindazole (0.05 g, 0.35 mmol) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH₂Cl₂: CH₃OH as eluant to provide 5 as a tan solid (0.03 g, 25%). ¹H NMR (CDCl₃, 400 MHz) δ 9.55 (s, 1H), 8.46 (s, 1H), 8.21 (s, 1H), 8.05 (m, 2H), 7.77 (m, 3H), 7.54 (m, 1H), 6.99 (d, J = 8 Hz, 2H), 4.74 (s, 2H).

Example 3:

Carboxylic acid 7, HOBt (0.10 g, .75 mmol), EDAC (0.15 g, 0.79 mmol), Et₃N (0.16 mL, 0.12 g, 1.15 mmol), DMF (5 mL) and sulfoxide 399 (0.15 g, 0.68 mmol) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford a tan solid (0.09 g, 34%). ¹H NMR (CDCl₃, 300 MHz) δ 9.14 (s, 1H), 8.00 (m, 2H), 7.80 (d, J = 3 Hz, 1H), 7.56 (m, 2H), 7.05 (d, J = 9

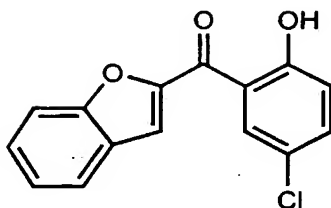
Hz, 2H), 6.87 (br s, 1H), 4.77 (s, 2H), 4.04 (m, 1H), 3.54 (m, 1H), 3.0 (m, 2H), 2.21 (s, 3H).

Example 4



9

Step A:



10

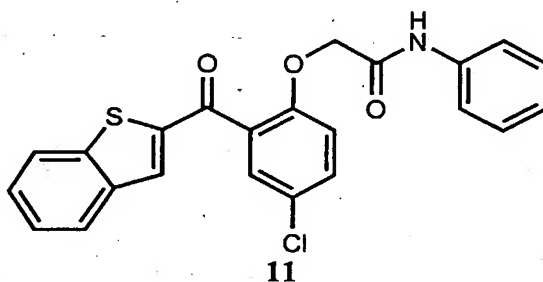
2-Benzofurancarboxylic acid (2.51 g, 15.48 mmol), CH_2Cl_2 (50 mL), DMF (4 drops), and oxalyl chloride (1.5 mL, 2.18 g, 17.19 mmol) were used to prepare the corresponding acid chloride according to general procedure V. The acid chloride was used immediately in combination with 4-chloroanisole (2.16 g, 15.15 mmol), AlCl_3 (3.01 g, 22.57 mmol) and CH_2Cl_2 (50 mL) according to general procedure I. Compound 10 was purified by flash chromatography using 7:3 hexane/ CH_2Cl_2 as eluant to provide 10 as a yellow solid (2.39 g, 57%). ^1H NMR (CDCl_3 , 300 MHz) δ 12.05 (s, 1H), 8.48 (d, $J=3\text{ Hz}$, 1H), 7.82 (d, $J=9\text{ Hz}$, 1H), 7.79 (s, 1H), 7.73 (d, $J=9\text{ Hz}$, 1H), 7.56 (m, 2H), 7.42 (t, $J=7.5\text{ Hz}$, 1H), 7.09 (d, $J=9\text{ Hz}$, 1H).

Step B:

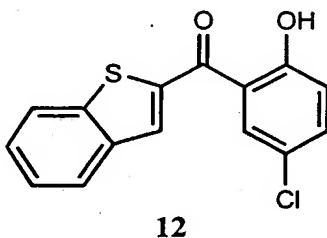
Into a round-bottom flask equipped with a stir bar, a reflux condenser and nitrogen on demand were placed phenol 10 (0.14 g, 0.51 mmol), 2'-chloroacetanilide (0.10 g, 0.59 mmol), K_2CO_3 (0.50 g, 3.62 mmol) and acetone (10 mL). The mixture was heated to reflux for 16 h, after which time it was allowed to cool to rt and was poured into a

separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to leave orange oil. The product was purified by flash chromatography using 4:1 hexane/ethyl acetate as eluant to provide 9 as a white solid (0.12 g, 58%). ^1H NMR (CDCl_3 , 300 MHz) δ 9.33 (s, 1H), 7.75 (m, 5H), 7.61 (m, 3H), 7.39 (m, 3H), 7.15 (m, 2H), 4.77 (s, 2H).

Example 5



Step A:



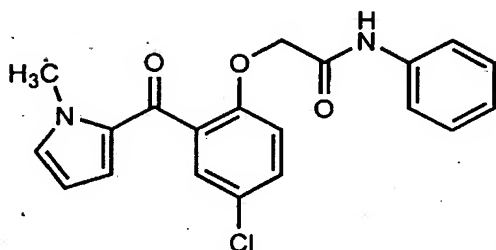
2-Benzothiophenecarboxylic acid (2.51 g, 14.08 mmol), CH_2Cl_2 (35 mL), DMF (4 drops), and oxalyl chloride (1.3 mL, 1.89 g, 14.9 mmol) were used to prepare the corresponding acid chloride according to general procedure V. The acid chloride was used immediately in combination with 4-chloroanisole (2.08 g, 14.59 mmol), AlCl_3 (3.15 g, 23.62 mmol) and CH_2Cl_2 (35 mL) according to general procedure I. Compound 12 was purified by flash chromatography using 7:3 hexane/ CH_2Cl_2 as eluant to provide a yellow solid (2.25 g, 55%). ^1H NMR (CDCl_3 , 300 MHz) δ 11.45 (s, 1H), 8.02 (m, 3H), 7.55 (m, 4H), 7.10 (d, $J = 9$ Hz, 1H).

Step B:

Into a round-bottom flask equipped with a stir bar, a reflux condenser and nitrogen on demand were placed phenol 12 (0.22 g, 1.23 mmol), 2'-chloroacetanilide (0.22 g, 1.30 mmol), K_2CO_3 (1.46 g, 10.6 mmol) and acetone (25 mL). The mixture was heated to

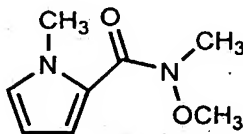
reflux for 16 h, after which time it was allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to leave orange oil. The product was purified by flash chromatography using 4:1 hexane/ethyl acetate as eluant to afford a white solid (0.27 g, 52%). ^1H NMR (CDCl_3 , 400 MHz) δ 9.16 (s, 1H), 7.90 (t, J = 10 Hz, 2H), 7.82 (s, 1H), 7.64 (m, 2H), 7.53 (m, 2H), 7.42 (t, J = 8 Hz, 1H), 7.30 (t, J = 8 Hz, 2H), 7.10 (t, J = 8 Hz, 1H), 7.04 (d, J = 8 Hz, 1H), 4.70 (s, 2H).

Example 6



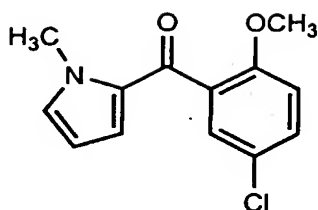
13

Step A:

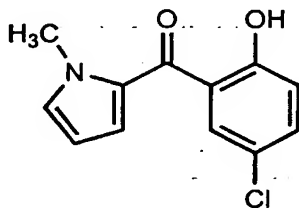


14

1-Methyl-2-pyrrolecarboxylic acid (4.75 g, 37.96 mmol), CH_2Cl_2 (100 mL), DMF (0.5 mL) and oxalyl chloride (3.6 mL, 5.24 g, 41.27 mmol) were used according to general procedure V. Into a separate flask were placed N,O -dimethylhydroxylamine hydrochloride (4.45 g, 45.62 mmol), Et_3N (26 mL, 19 g, 187 mmol) and chloroform (100 mL). The resulting solution was cooled to 0 °C and the acid chloride (in 20 mL of chloroform) was added dropwise. The resulting mixture was allowed to stir at 0 °C for an additional 1 h, after which time it was allowed to warm to RT. The mixture was then poured into a separatory funnel containing chloroform and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to afford a brown oil which was used in subsequent reactions with no further purification. ^1H NMR (CDCl_3 , 300 MHz) δ 6.95 (m, 1H), 6.78 (m, 1H), 6.15 (m, 1H), 3.94 (s, 3H), 3.73 (s, 3H), 3.36 (s, 3H).

Step B:**15**

- 5 To a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (5.97 g, 26.95 mmol) and THF (75 mL). The resulting solution was cooled to -78°C and n-butyl lithium (19.5 mL of a 1.6 M solution in hexane, 31.2 mmol) was added via syringe. The resulting solution was allowed to stir at -78°C for 30 min and amide 14 (4.2 g, 24.97 mmol in 15 mL THF), was added via syringe. The mixture was
10 allowed to stir at -78°C for 30 min, after which time it was allowed to warm to RT and stir for an additional 30 min. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to afford a viscous, clear oil which was used in subsequent reactions without any
15 further purification.

Step C:**16**

- To a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 15 (2.19 g, 8.77 mmol) and CH_2Cl_2 (80 mL). The solution was cooled to -78°C and boron tribromide (43 mL of a 1.0 M solution in CH_2Cl_2 , 43 mmol) was added via syringe. The resulting dark red mixture was allowed to warm to rt and stir for 2 h. The mixture was then carefully poured over ice water, giving a two-phase mixture, which was allowed to stir for 30 min. It was then poured into a separatory funnel containing water. The organic layer
25 was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to afford a yellow solid (1.56 g, 75%) which was used in subsequent reactions without any further purification. ^1H NMR (CDCl_3 ,

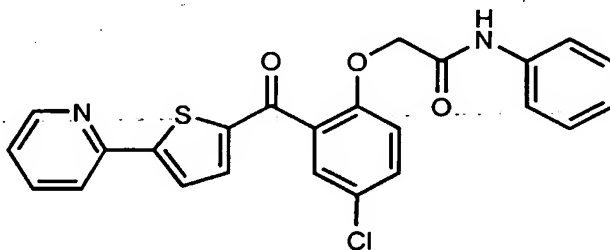
300 MHz) δ 11.65 (s, 1H), 7.90 (d, J = 3 Hz, 1H), 7.43 (dd, J = 9, 3 Hz, 1H), 7.02 (m, 2H), 6.91 (m, 1H), 6.28 (m, 1H), 4.01 (s, 3H).

Step D:

5

Into a round-bottom flask equipped with a stir bar, a reflux condenser and nitrogen on demand were placed phenol 16 (0.15 g, 0.64 mmol), 2'-chloroacetanilide (0.13 g, 0.78 mmol), K_2CO_3 (0.47 g, 3.39 mmol) and acetone (10 mL). The resulting mixture was heated to reflux for 18 h, after which time it was allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 4:1 hexane/ethyl acetate to afford 13 as a white solid (0.18 g, 77%). 1H NMR ($CDCl_3$, 300 MHz) δ 9.69 (s, 1H), 7.81 (d, J = 9 Hz, 2H), 7.54 (d, J = 3 Hz, 1H), 7.47 (dd, J = 6, 3 Hz, 1H), 7.38 (t, J = 6 Hz, 2H), 7.16 (t, J = 6 Hz, 1H), 7.03 (m, 2H), 6.75 (m, 1H), 6.23 (m, 1H), 4.75 (s, 2H), 4.17 (s, 3H).

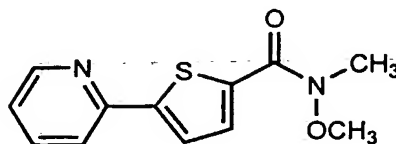
Example 7



20

17

Step A:

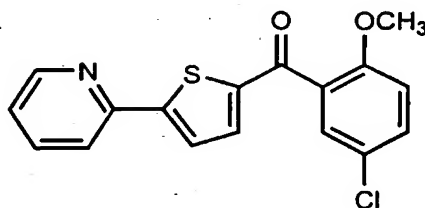


25

18

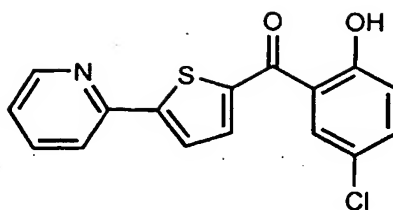
5-(2-pyridyl)thiophene-2-carboxylic acid (2.62 g, 12.77 mmol), oxalyl chloride (1.4 mL, 2.04 g, 16.05 mmol), DMF (0.25 mL) and CH_2Cl_2 (25 mL) were used according to general procedure V. The acid chloride was used immediately in the next step without any further purification. Into a separate flask equipped with a stir bar and nitrogen on demand were

placed N,O-dimethylhydroxylamine hydrochloride (1.63 g, 16.71 mmol), Et₃N (9 mL, 6.53 g, 64.57 mmol) and CH₂Cl₂ (25 mL). The resulting solution was cooled to 0 °C, and the acid chloride (in 10 mL of CH₂Cl₂) was added dropwise. When the addition was complete, the mixture was allowed to stir at 0 °C for an additional 30 min, and then was allowed to warm to rt and stir for an additional 1 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure leaving a white solid (2.69 g, 85%). The product was used in subsequent steps without any further purification. ¹H NMR (CDCl₃, 300 MHz) δ 8.64 (d, J = 3 Hz, 1H), 8.00 (d, J = 3 Hz, 1H), 7.75 (m, 2H), 7.60 (d, J = 6 Hz, 1H), 7.26 (m, 1H), 3.88 (s, 3H), 3.43 (s, 3H).

Step B:**19**

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (2.42 g, 10.93 mmol) and THF (35 mL). The solution was cooled to -78 °C and n-butyl lithium (7.5 mL of a 1.6 M solution in hexane, 12 mmol) was added via syringe. The resulting yellowish mixture was allowed to stir at -78 °C for 30 min, after which time amide 18 (2.25 g, 9.06 mmol) in THF (10 mL) was added slowly. The resulting mixture was allowed to stir at -78 °C for 30 min and it was then allowed to warm to rt and stir for an additional 1 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure. The product was further purified by flash chromatography using 7:3 hexane/ethyl acetate to afford a yellow solid (1.42 g, 48%). ¹H NMR (CDCl₃, 300 MHz) δ 8.66 (d, J = 6 Hz, 1H), 7.79 (m, 2H), 7.64 (d, J = 6 Hz, 1H), 7.56 (d, J = 6 Hz, 1H), 7.45 (m, 2H), 7.30 (m, 2H), 6.18 (d, J = 6 Hz, 1H), 3.84 (s, 3H).

Step C:



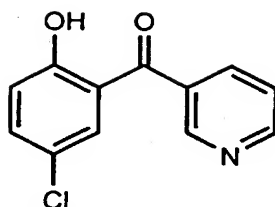
20

Into a round-bottom flask equipped with a stir bar, and nitrogen on demand were placed ketone 19 (1.42 g, 4.31 mmol) and CH_2Cl_2 (70 mL). The mixture was cooled to -78°C and boron tribromide (20 mL of a 1.0 M solution in CH_2Cl_2 , 20 mmol) was added via syringe. The resulting dark red mixture was allowed to stir at -78°C for 1 h and it was then allowed to warm to rt and stir for an additional 1 h. The mixture was carefully poured over ice water and the resulting two-phase mixture was allowed to stir for 30 min. It was then poured into a separatory funnel containing CH_2Cl_2 and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to afford a tan solid (1.32 g, 97%). ^1H NMR (CDCl_3 , 300 MHz) δ 11.55 (s, 1H), 8.70 (d, $J=6$ Hz, 1H), 8.00 (d, $J=3$ Hz, 1H), 7.82 (m, 3H), 7.75 (d, $J=3$ Hz, 1H), 7.51 (dd, $J=9, 3$ Hz, 1H), 7.34 (m, 1H), 7.08 (d, $J=9$ Hz, 1H).

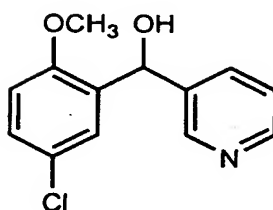
Step D:

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed phenol 20 (0.13 g, 0.42 mmol), 2'-chloroacetanilide (0.10 g, 0.57 mmol), K_2CO_3 (0.29 g, 2.09 mmol) and acetone (10 mL). The resulting mixture was heated to reflux for 18 h, after which time it was allowed to cool to RT and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 65:35 hexane/ethyl acetate as eluant to afford 17 as a white solid (0.16 g, 85%). ^1H NMR (CDCl_3 , 300 MHz) δ 9.34 (s, 1H), 8.70 (d, $J=6$ Hz, 1H), 7.80 (m, 3H), 7.68 (m, 3H), 7.55 (dd, $J=9, 3$ Hz, 1H), 7.35 (m, 4H), 7.14 (t, $J=6$ Hz, 1H), 7.07 (d, $J=9$ Hz, 1H), 4.75 (s, 2H).

84

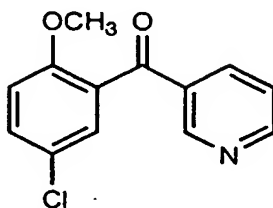


21

Step A:

22

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (7.02 g, 31.69 mmol) and diethyl ether (Et₂O, 75 mL). The resulting solution was cooled to -78 °C and n-butyl lithium (21 mL of a 1.6 M solution in hexane, 33.6 mmol) was added via syringe. The resulting mixture was allowed to stir at -78 °C for 15 min, after which time 3-pyridinecarboxaldehyde (3.73 g, 34.82 mmol) was added slowly. The resulting solution was allowed to stir at -78 °C for 30 min after which time it was allowed to warm to RT and stir for an additional 30 min. The mixture was poured into a separatory funnel containing Et₂O and water. The organic layer was collected and was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to afford a clear, viscous oil (6.97 g, 88%) which was used without any further purification. ¹H NMR (CDCl₃, 300 MHz) δ 8.65 (s, 1H), 8.53 (d, J= 3Hz, 1H), 7.80 (d, J= 9 Hz, 1H), 7.40 (d, J= 3 Hz, 1H), 7.31 (m, 3H), 6.84 (d, J= 9 Hz, 1H), 6.10 (s, 1H), 3.82 (s, 3H).

Step B:

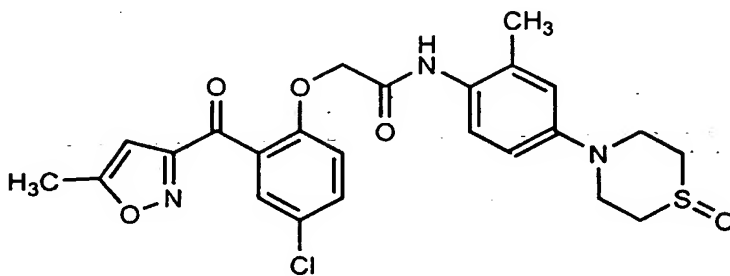
23

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed alcohol **22** (6.97 g, 28 mmol), manganese dioxide (MnO_2 , 20.27 g, 233 mmol) and CHCl_3 (200 mL). The resulting suspension was heated to reflux for 1 h, after which time it was allowed to cool to rt. The suspension was then filtered through a pad of celite, which was washed with several portions of CH_2Cl_2 . The solvents were removed under reduced pressure to afford a tan solid (6.55 g, 95%). The solid was used in subsequent reactions without any further purification. ^1H NMR (CDCl_3 , 300 MHz) δ 8.94 (d, J = 3 Hz, 1H), 8.81 (dd, J = 6, 3 Hz, 1H), 8.19 (m, 1H), 7.49 (m, 2H), 6.98 (d, J = 9 Hz, 1H), 3.74 (s, 3H).

10 **Step C:**

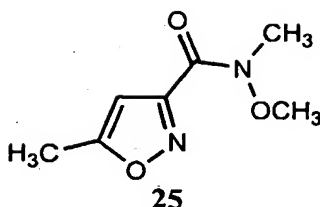
Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed ketone **23** (6.55 g, 26.45 mmol) and CH_2Cl_2 (200 mL). The resulting solution was cooled to -78°C and boron tribromide (50 mL of a 1.0 M solution in CH_2Cl_2 , 50 mmol) was added via syringe. The resulting solution was allowed to stir at -78°C for 1 h, after which time it was allowed to warm to rt and stir for an additional 30 min. The mixture was carefully poured over ice water and the resulting two-phase system was stirred for 30 min. It was then poured into a separatory funnel containing water and CH_2Cl_2 . The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to afford **21** as a yellow solid (5.25 g, 85%). ^1H NMR (CDCl_3 , 300 MHz) δ 11.77 (s, 1H), = 3 Hz, 1H), 8.90 (dd, J = 3, 1.5 Hz, 1H), 8.07 (m, 1H), 7.55 (m, 3H), 7.11 (m, 1H).

Example 9:

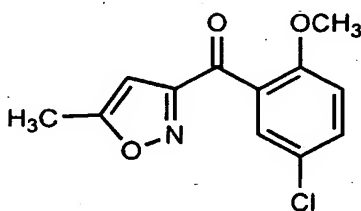


Step A:

86

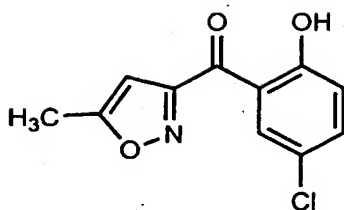


Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed N,O-dimethylhydroxylamine hydrochloride (7.79 g, 79.86 mmol), Et₃N (24 mL, 172.2 mmol) and CHCl₃ (150 mL). The resulting solution was cooled to 0 °C and 5-Methyl-3-isoxazolecarbonyl chloride (10.0 g, 68.70 mmol) in CHCl₃ (15 mL) was added dropwise, after which the resulting solution was allowed to stir at 0 °C for 1h. The mixture was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to afford a clear oil (10.53 g, 90%). ¹H NMR (CDCl₃, 400 MHz) δ 6.92 (s, 1H), 3.75 (br s, 6 H), 2.44 (s, 3H).

Step B:

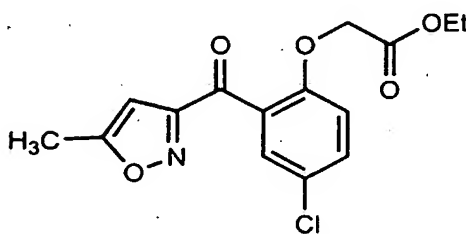
Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (5.02 g, 22.66 mmol) and Et₂O (150 mL). The solution was cooled to -78 °C and n-butyl lithium (15.6 mL of a 1.6 M solution in hexane, 24.96 mmol) was added via syringe. The resulting solution was allowed to stir at -78 °C for 15 min and then amide 25 (4.03 g, 23.68 mmol) in Et₂O (20 mL) was added slowly, after which time the solution was allowed to stir at -78 °C for 30 min. It was then allowed to warm to rt and stir for an additional 2 h. The mixture was then poured over ice water and the two-phase system was stirred for 30 min. It was then poured into a separatory funnel containing Et₂O and water. The organic layer was collected and was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to provide a white solid (5.37 g, 94%). ¹H NMR (CDCl₃, 400 MHz) δ 7.51 (d, J = 3 Hz, 1H), 7.42 (dd J = 6, 3 Hz, 1H), 6.92 (d, J = 6 Hz, 1H), 6.45 (s, 1H), 3.76 (s, 3H), 2.49 (s, 3H).

87

Step C:

27

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed ketone **26** (5.36 g, 21.30 mmol) and CH_2Cl_2 (100 mL). The solution was cooled to -78°C and boron tribromide (40 mL of a 1.0 M solution in CH_2Cl_2) was added via syringe. The resulting dark red solution was allowed to stir at -78°C for 1 h, after which time it was allowed to warm to RT and stir for an additional 2 h. The mixture was then carefully poured over ice water and the resulting two-phase system was stirred for 30 min. The mixture was then poured into a separatory funnel containing Et_2O and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to afford a tan solid (5.44 g) which was used in subsequent reactions without any further purification.

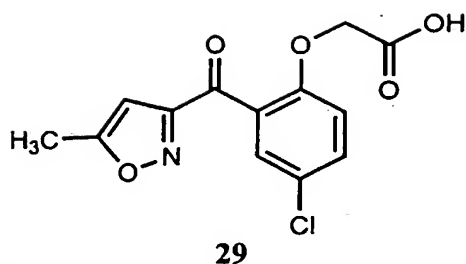
Step D:

28

Phenol **27** (5.44 g crude weight, 21 mmol), ethyl bromoacetate (2.3 mL, 20.74 mmol), K_2CO_3 (12.32 g, 89.14 mmol) and acetone (150 mL) were used according to general procedure II. The product was used in subsequent reactions without any further purification.

Step E:

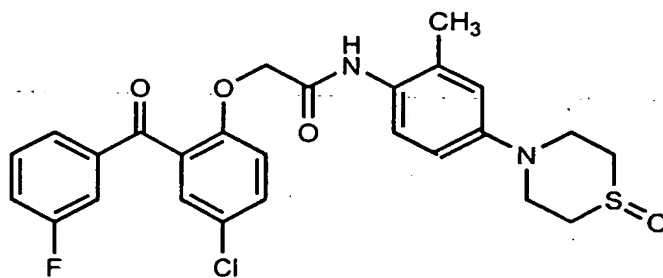
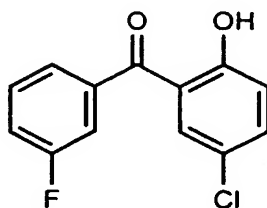
88



Ester **28** (21 mmol), THF (35 mL), EtOH (15 mL), water (15 mL) and LiOH (2.04 g, 48.62 mmol) were used according to general procedure III. Trituration with hexane provided **29** as a white foam, which was used in subsequent reactions without any further purification.

Step F:

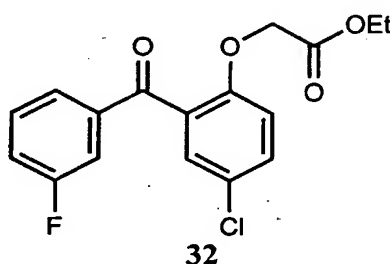
Acid **29** (0.215 g, 0.727 mmol), HOBt (0.112 g, 0.829 mmol), EDAC (0.198 g, 1.03 mmol), Et₃N (0.25 mL, 1.79 mmol), DMF (5 mL) and sulfoxide **399** (0.198 g, 0.884 mmol) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH₂Cl₂/CH₃OH as eluant to afford **24** as a tan solid (0.124 g, 34%). ¹H NMR (CDCl₃, 400 MHz) δ 8.78 (s, 1H), 7.77 (d, J = 4 Hz, 1H), 7.53-7.47 (m, 2H), 6.97 (d, J = 8 Hz, 1H), 6.80 (m, 2H), 6.49 (s, 1H), 4.69 (s, 2H), 3.98-3.92 (m, 2H), 3.53 (m, 2H), 2.94-2.84 (m, 4H), 2.18 (s, 3H), 1.55 (s, 3H).

Example 10:**Step A:**

31

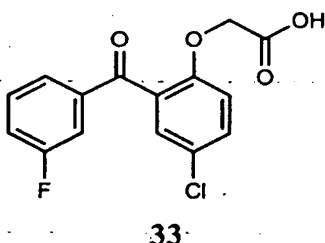
4-Chloroanisole (4.06 g, 28.47 mmol), 3-fluorobenzoyl chloride (4.53 g, 28.57 mmol), AlCl_3 (6.23 g, 46.72 mmol) and CH_2Cl_2 (100 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/ CH_2Cl_2 as eluant to provide the 31 as a yellow solid (2.60 g, 36%). ^1H NMR (CDCl_3 , 300 MHz) δ 11.80 (s, 1H), 7.50 (m, 6H), 7.09 (d, $J=9$ Hz, 1H).

Step B:



Phenol 31 (2.60 g, 10.37 mmol), ethyl bromoacetate (1.3 mL, 11.72 mmol), K_2CO_3 (7.15 g, 51.73 mmol), and acetone (80 mL) were used according to general procedure II. The product was used in subsequent reactions without any further purification.

Step C:



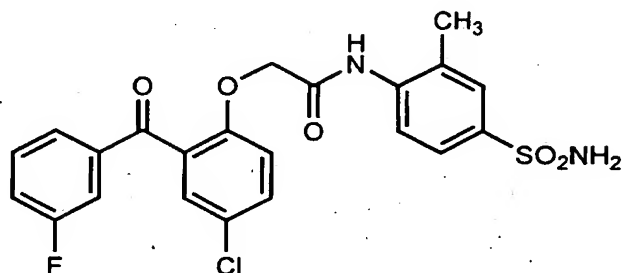
Ester 32 (10 mmol), THF (30 mL), EtOH (10 mL), water (10 mL) and LiOH (1.02 g, 24.31 mmol) were used according to general procedure III to afford 33 as a white solid (3.01 g, 98%). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 7.71-7.38 (m, 6H), 6.91 (d, $J=9$ Hz, 1H), 4.26 (s, 2H).

Step D:

25 Acid 33 (0.22 g, 0.71 mmol), HOBt (0.115 g, 0.851 mmol), EDAC (0.205 g, 1.07 mmol) Et_3N (0.25 mL, 1.79 mmol), DMF (5 mL) and sulfoxide 399 (0.185 g, 0.826 mmol) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ as eluant to provide 30 as a white solid (0.05

g, 14%). ^1H NMR (CDCl_3 , 400 MHz) δ 8.21 (s, 1H), 7.58-7.38 (m, 6H), 7.28 (m, 1H), 7.01 (d, $J = 8$ Hz, 1H), 6.76 (m, 2H), 4.66 (s, 2H), 3.98-3.91 (m, 2H), 3.53 (m, 2H), 2.91-2.83 (m, 4H), 1.54 (s, 3H).

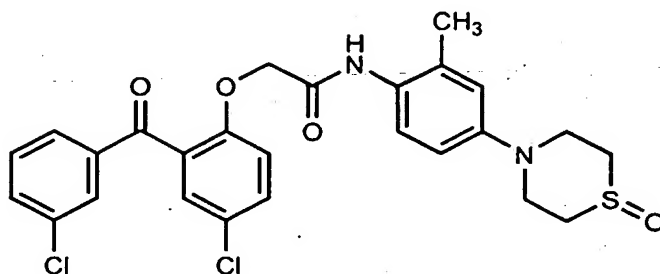
5 **Example 11:**



34

Carboxylic acid 33 (0.224 g, 0.726 mmol), oxalyl chloride (0.2 mL, 2.29 mmol), and CH_2Cl_2 (4 mL) were used according to general procedure V. Into a separate flask were placed sulfonamide 466 (0.158 g, 0.848 mmol), Et_3N (0.25 mL, 1.79 mmol) and acetonitrile (CH_3CN , 8 mL). The mixture was cooled to 0°C and the acid chloride (in 2 mL CH_3CN) was added dropwise over several minutes. The resulting mixture was allowed to stir at 0°C for 30 min, after which time it was allowed to warm to RT and stir for an additional 5 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 95:5 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ as eluant to provide 34 as a white solid (0.117 g, 34%). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 9.39 (s, 1H), 7.71-7.52 (m, 9H), 7.31-7.27 (m, 3H), 4.85 (s, 2H), 2.21 (s, 3H).

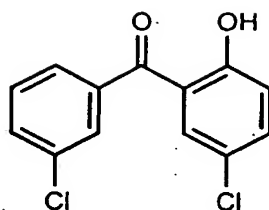
20 **Example 12:**



35

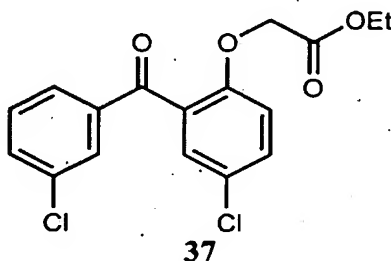
25 **Step A:**

91



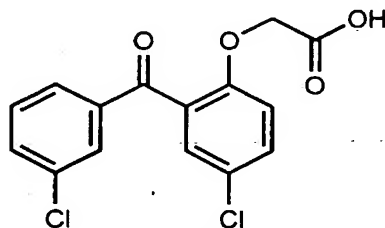
36

4-Chloroanisole (4.02 g, 28.19 mmol), 3-chlorobenzoyl chloride (3.8 mL, 4.94 g, 28.22 mmol), AlCl_3 (5.62 g, 42.15 mmol) and CH_2Cl_2 (75 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/ CH_2Cl_2 as eluant to provide 36 as a yellow solid (5.35 g, 71%). ^1H NMR (CDCl_3 , 400 MHz) δ 1.72 (s, 1H), 7.64 (s, 1H), 7.58 (d, J = 8 Hz, 1H), 7.53-7.44 (m, 4H), 7.03 (d, J = 12 Hz, 1H).

Step B:

37

Phenol 36 (5.35 g, 20.03 mmol), ethyl bromoacetate (2.5 mL, 22.54 mmol), K_2CO_3 (12.91 g, 93.41 mmol), and acetone (125 mL) were used according to general procedure II. The product was used in subsequent reactions without any further purification.

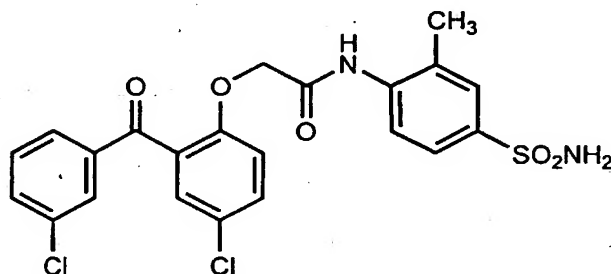
Step C:

38

Ester 37 (20 mmol), THF (60 mL), EtOH (15 mL), water (15 mL) and LiOH (2.09 g, 49.81 mmol) were used according to general procedure III. The product was used in subsequent reactions without any further purification.

Step D:

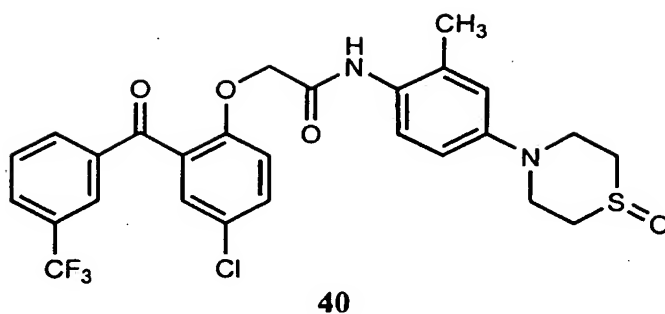
Carboxylic acid **38** (0.29 g, 0.892 mmol), sulfoxide **399** (0.24 g, 1.07 mmol), EDAC (0.261 g, 1.36 mmol), HOBT (0.142 g, 1.05 mmol) and DMF (7 mL) were used according to general procedure IV, with the exception that no Et₃N was used. The product was purified by flash chromatography using 97:3 CH₂Cl₂/CH₃OH as eluant to provide **35** as a tan solid (0.34 g, 72%). ¹H NMR (CDCl₃, 300 MHz) δ 8.21 (s, 1H), 7.86 (d, J = 3 Hz, 1H), 7.72 (d, J = 6 Hz, 1H), 7.60-7.43 (m, 4H), 7.07 (d, J = 9 Hz, 2H), 6.85-6.82 (m, 3H), 4.72 (s, 2H), 4.06-3.98 (m, 2H), 3.62-3.55 (m, 2H), 3.00-2.90 (m, 4H), 2.18 (s 3H).

Example 13:

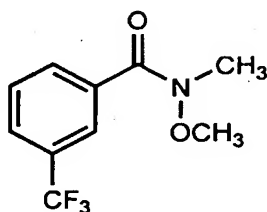
Carboxylic acid **38** (0.229 g, 0.704 mmol), oxalyl chloride (0.2 mL, 2.29 mmol) and CH₂Cl₂ (4 mL) were used according to general procedure V. Into a separate flask were placed sulfonamide **466** (0.156 g, 0.838 mmol), Et₃N (0.25 mL, 1.79 mmol) and CH₃CN (8 mL). The acid chloride (in 2 mL of CH₃CN) was added dropwise over several minutes. The resulting solution was allowed to stir at 0 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 5 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 95:5 CH₂Cl₂/CH₃OH as eluant to provide **39** as a white solid (0.110 g, 32%). ¹H NMR (DMSO-d₆, 300 MHz) δ 9.39 (s, 1H), 7.82-7.53 (m, 9H), 7.30 (m, 3H), 4.84 (s, 2H), 2.20 (s, 3H).

Example 14:

93

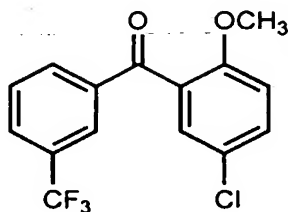


40

Step A:

41

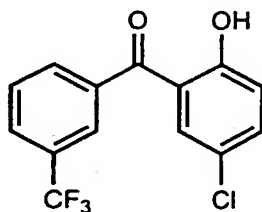
Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed N,O-dimethylhydroxylamine hydrochloride (3.16 g, 32.40 mmol), Et₃N (9 mL, 64.57 mmol) and CHCl₃ (85 mL). The solution was cooled to 0 °C and 3-trifluoromethylbenzoyl chloride (4 mL, 5.53 g, 26.52 mmol) was added dropwise over several minutes. The resulting solution was allowed to stir at 0 °C for 30 min, after which time it was allowed to warm to RT and stir for an additional 30 min. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to provide a clear oil which was used without any further purification.

Step B:

42

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (5.23 g, 23.61 mmol) and Et₂O (100 mL). The solution was cooled to -78 °C and n-butyl lithium (17 mL of a 1.6 M solution in hexane, 27.2 mmol) was added dropwise. The resulting mixture was allowed to stir at -78 °C for 15 min, after which time amide 41 (5.56 g, 23.84 mmol) was added dropwise. The mixture was allowed to stir at -78 °C for 30 min, after which time it was allowed to warm to RT and stir for an additional 2 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to leave a yellow oil, which was used in subsequent reactions without any further purification

Step C:

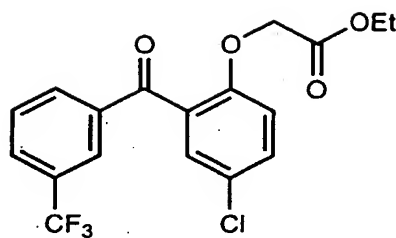


43

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 42 (23 mmol) and CH₂Cl₂ (150 mL). The solution was cooled to -78 °C and boron tribromide (35 mL of a 1.0 M solution in CH₂Cl₂, 35 mmol) was added dropwise over several minutes. The resulting dark mixture was allowed to stir at -78 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 1h. The mixture was carefully poured over ice and the two-phase mixture was stirred for 30 min. It was then poured into a separatory funnel containing CH₂Cl₂ and water. The organic layer was collected, washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to afford a yellow solid (5.04 g, 73%). ¹H NMR (CDCl₃, 300 MHz) δ 11.76 (s, 1H), 8.25-7.84 (m, 3H), 7.73 (t, J= 9 Hz, 1H), 7.56-7.52 (m, 2H), 7.12 (d, J= 9 Hz, 1H).

Step D:

95

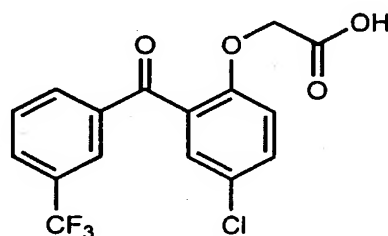


44

Phenol 43 (5.04 g, 16.76 mmol), ethyl bromoacetate (2.1 mL, 18.94 mmol), K_2CO_3 (9.01 g, 65.19 mmol) and acetone (100mL) were used according to general procedure II.

- 5 Removal of the solvents under reduced pressure afforded 44 as an oil (6.28 g, crude weight), which was used in subsequent reactions without any further purification.

Step E:



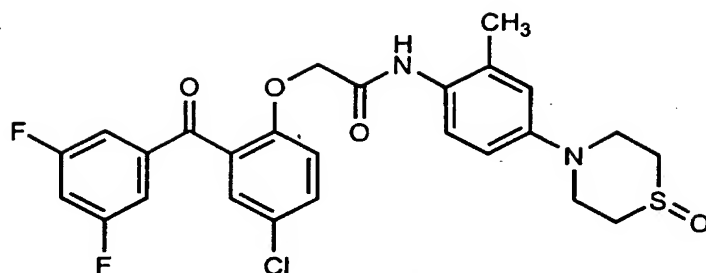
45

- 10 Ester 44 (6.28 g, crude weight, 16.24 mmol), THF (50 mL), water (25 mL) and EtOH (25 mL) were used according to general procedure IV. Removal of the solvents under reduced pressure provided acid 45 as a white solid (2.81 g, 48%) which was used without any further purification.

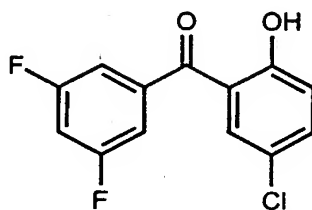
15 **Step F:**

Carboxylic acid 45 (0.208 g, 0.58 mmol), sulfoxide 399 (0.152 g, 0.679 mmol), EDAC (0.19 g, 0.991 mmol), HOBt (0.103 g, 0.76 mmol) and DMF (5 ML) were used according to general procedure IV. The product was purified by flash chromatography using 95:5

- 20 CH_2Cl_2/CH_3OH to provide 40 as an off-white solid (0.23 g, 70%). 1H NMR ($CDCl_3$, 300 MHz) δ 8.19 (d, J = 9 Hz, 2H), 8.01 (d, J = 9 Hz, 1H), 7.88 (d, J = 9 Hz, 1H), 7.66 (t, J = 6 Hz, 1H), 7.60 (dd, J = 9, 3 Hz, 1H), 7.50 (d, J = 9 Hz, 1H), 7.44 (d, J = 3 Hz, 1H), 7.09 (d, J = 9 Hz, 1H), 6.83 (m, 3H), 4.72 (s, 2H), 4.05-3.96 (m, 2H), 3.62-3.54 (m, 2H), 3.0-2.89 (m, 4H), 2.16 (s, 3H).

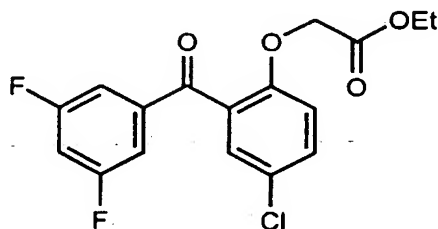
Example 15:

46

Step A:

47

4-Chloroanisole (4.12 g, 28.89 mmol), 3,5-difluorobenzoyl chloride (5.0 g, 28.3 mmol), AlCl_3 (5.65 g, 42.37 mmol) and CH_2Cl_2 (75 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/ CH_2Cl_2 as eluant to provide a yellow solid (2.72 g, 36%). ^1H NMR (CDCl_3 , 300 MHz) δ 11.64 (s, 1H), 7.54 (m, 2H), 7.23 (m, 2H), 7.11 (m, 2H).

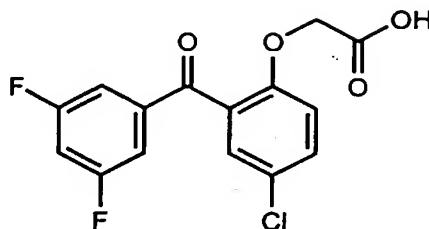
Step B:

48

Phenol 47 (2.72 g, 10.13 mmol), ethyl bromoacetate (1.3 mL, 11.7 mmol), K_2CO_3 (5.28 g, 38.2 mmol) and acetone (100 mL) were used according to general procedure II. Removal

of the solvents under reduced pressure afforded 48 as a clear oil (3.8 g, crude weight) that was used without any further purification.

Step C:



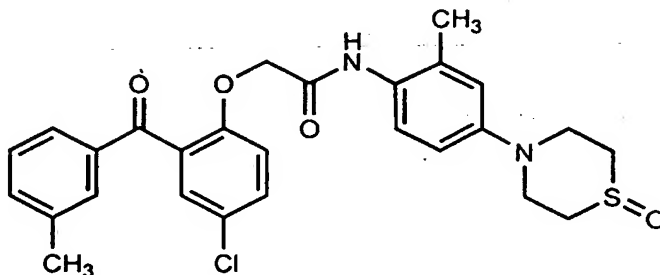
49

Ester 48 (10 mmol), THF (50 mL), water (25 mL) and EtOH (25 mL) were used according to general procedure III. Removal of the solvents under reduced pressure afforded 49 as a white solid, which was used in subsequent reactions without any further purification.

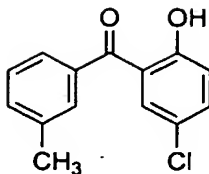
Step D:

Carboxylic acid 49 (0.20 g, 0.612 mmol), sulfoxide 399 (0.167 g, 1.22 mmol), EDAC (0.23 g, 1.2 mmol), HOBt (0.106 g, 0.784 mmol) and DMF (5 mL) were used according to general procedure IV, with the exception that no Et₃N was used. The product was purified by flash chromatography using 95:5 CH₂Cl₂/CH₃OH as eluant, followed by trituration with Et₂O, afforded 46 as an off-white solid (0.24 g, 74%). ¹H NMR (CDCl₃, 300 MHz) δ 8.29 (s, 1H), 7.61-7.54 (m, 2H), 7.42 (d, J = 3 Hz, 1H), 7.38 (m, 1H), 7.08 (m, 2H), 6.85 (m, 2H), 4.73 (s, 2H), 4.73 (, 2H), 4.05-3.96 (m, 2H), 3.62-3.55 (m, 2H), 2.94-2.89 (m, 4H), 2.21 (s, 3H).

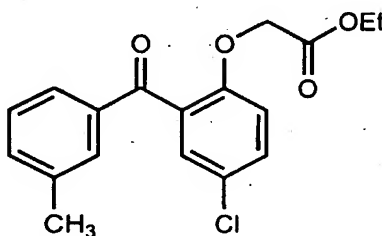
Example 16



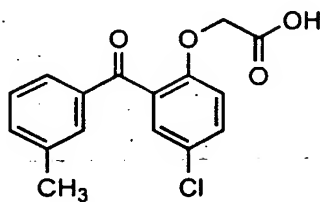
50

Step A:

4-Chloroanisole (4.16 g, 29.17 mmol), 3-methylbenzoyl chloride (4.42 g, 28.59 mmol), AlCl_3 (6.12 g, 45.9 mmol) and CH_2Cl_2 (150 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/ CH_2Cl_2 as eluant to provide **50** as yellow solid (1.54 g, 22%). ^1H NMR (CDCl_3 , 400 MHz) δ 11.91 (s, 1H), 7.54 (d, $J=4$ Hz, 1H), 7.47-7.39 (m, 5H), 7.02 (d, $J=8$ Hz, 1H), 2.44 (s, 3H).

Step B:**51**

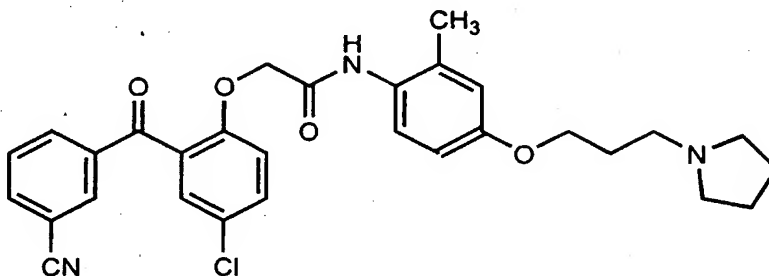
Phenol **50** (1.54 g, 6.24 mmol), ethyl bromoacetate (0.8 mL, 7.21 mmol), K_2CO_3 (3.15 g, 22.79 mmol) and acetone (35 mL) were used according to general procedure II. Removal of the solvents under reduced pressure afforded **51** as a clear oil that was used without any further purification.

Step C:**52**

Ester **51** (6.3 mmol), lithium hydroxide (0.700 g, 16.68 mmol), THF (20 mL), water (10 mL) and EtOH (10 mL) were used according to general procedure III. Removal of the solvents under reduced pressure afforded **52** as a white solid (1.82 g, 96%) which was used without any further purification.

Step D:

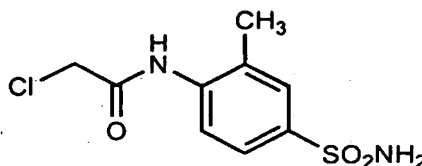
Carboxylic acid **52** (0.21 g, 0.70 mmol), sulfoxide 399 (0.19 g, 0.853 mmol), EDAC
5 (0.212 g, 1.11 mmol), HOBt (0.121 g, 0.895 mmol) and DMF (5 mL) were used according
to general procedure IV, with the exception that no Et₃N was used. The product was
purified by flash chromatography using 95:5 CH₂Cl₂/CH₃OH as eluant to provide **50** as an
off-white solid (0.09 g, 25%). ¹H NMR (CDCl₃, 300 MHz) δ 8.13 (s, 1H), 7.69-7.30 (m,
8H), 7.04 (d, J = 9 Hz, 1H), 6.81 (m, 3H), 4.69 (s, 2H), 4.05-3.96 (m, 2H), 3.60-3.51 (m,
10 2H), 2.93-2.85 (m, 4H), 2.38 (s, 3H), 2.14 (s, 3H).

Example 17

15

53

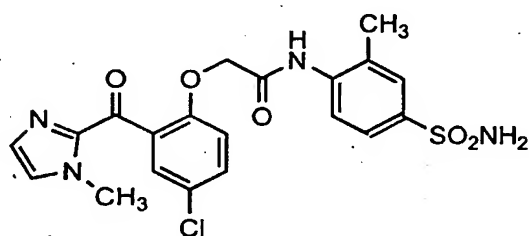
Carboxylic acid **129** (0.316 g, 1.00 mmol), amine **143** (0.241 g, 1.03 mmol), EDAC (0.251
g, 1.31 mmol), HOBt (0.167 g, 1.24 mmol) and DMF (5 mL) were used according to
general procedure IV, with the exception that no Et₃N was used. The product was purified
by flash chromatography using 9:1 CHCl₃/CH₃OH as eluant to provide **53** as a tan powder
20 (0.082 g, 15%).

**54**

Into a round-bottom flask were placed aniline **466** (0.246 g, 1.32 mmol), Et₃N (0.9 mL,
0.65 g, 6.5 mmol), CHCl₃ (5 mL) and CH₃CN (5 mL). The resulting mixture was cooled to
25 0 °C and 2'-chloroacetyl chloride (0.2 mL, 2.51 mmol) was added dropwise over several

minutes. The mixture was allowed to stir at 0 °C for 30 minutes and was then allowed to warm to rt and stir for an additional 30 minutes. The mixture was then poured into a separatory funnel containing H₂O and ethyl acetate. The organic layer was collected, washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to afford a dark, green oil. Several portions of hexane were added and subsequently removed under reduced pressure to afford **54** as a green solid, which was used without any further purification. ¹H NMR (DMSO-d₆, 300 MHz) δ 9.84 (s, D 1H), 7.69 (m, 3H), 7.31 (s, 2H), 4.38 (s, 2H), 2.31 (s, 3H).

Example 18

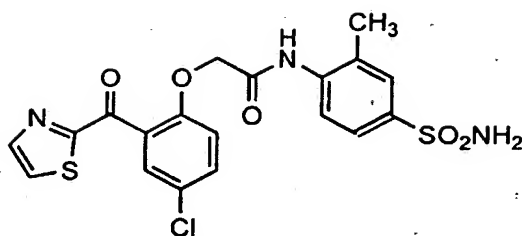


55

Into a round-bottom flask were placed amine **54** (0.16 g, 0.61 mmol), phenol **185** (0.14 g, 0.60 mmol), K₂CO₃ (0.66 g, 4.8 mmol) and acetone (10 mL). The resulting mixture was allowed to heat to reflux and stir overnight. The mixture was then allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected, washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 95:5 CH₂Cl₂/CH₃OH to provide **55** as an off-white solid (0.02 g, 7%). ¹H NMR (DMSO-d₆, 400 MHz) δ 9.74 (s, 1H), 7.63-7.53 (m, 4H), 7.26-7.19 (m, 4H), 6.97 (s, 2H), 4.81 (s, 2H), 3.99 (s, 3H), 2.08 (s, 3H).

Example 19

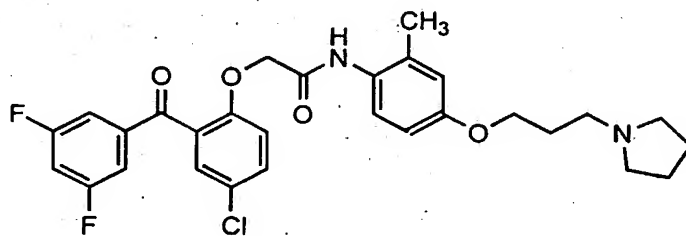
101



56

Into a round-bottom flask were placed amine **54** (0.16 g, 0.62 mmol), K_2CO_3 (0.51 g, 3.7 mmol), phenol **4** (0.22 g, 0.90 mmol) and acetone (5 mL). The same procedure was followed as in example 55. The product was purified by flash chromatography using 97:3 $CHCl_3/CH_3OH$ to provide **56** as a tan solid (0.03 g, 10%). 1H NMR ($DMSO-d_6$, 300 MHz) δ 9.39 (s, 1H), 8.33 (d, $J = 3$ Hz, 1H), 8.16 (d, $J = 3$ Hz, 1H), 7.83-7.64 (m, 5H), 7.39-7.30 (m, 3H), 4.86 (s, 2H), 2.23 (s, 3H).

10 Example 20

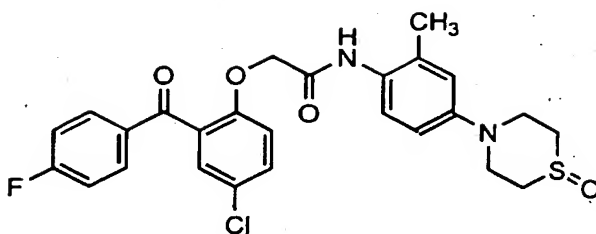


57

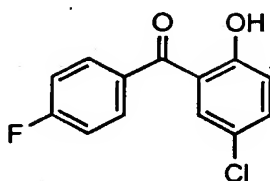
Acid **49** (0.351 g, 1.07 mmol), amine **143** (0.253 g, 1.08 mmol), EDAC (0.341 g, 1.78 mmol), HOBt (0.193 g, 1.43 mmol) and DMF (7 mL) were used according to general procedure IV, with the exception that no Et_3N was used. The product was purified by flash chromatography using 9:1 $CHCl_3/CH_3OH$ to provide a tan solid (0.09 g, 15%). 1H NMR ($CDCl_3$, 300 MHz) δ 8.19 (s, 1H), 7.49 (dd, $J = 9, 3$ Hz, 1H), 7.42 (d, $J = 9$ Hz, 1H), 7.33 (d, $J = 3$ Hz, 1H), 7.27 (d, $J = 3$ Hz, 1H), 7.19 (m, 1H), 7.01-6.96 (m, 2H), 6.65-6.63 (m, 2H), 4.62 (s, 2H), 4.00-3.96 (t, $J = 6$ Hz, 2H), 3.76 (m, 2H), 3.23-3.15 (m, 2H), 2.75 (m, 2H), 2.39-2.12 (m, 6H), 2.09 (s, 3H).

Example 21

102

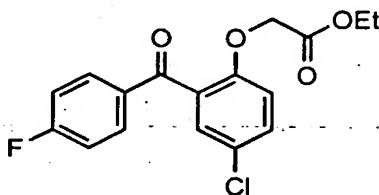


58

Step A:

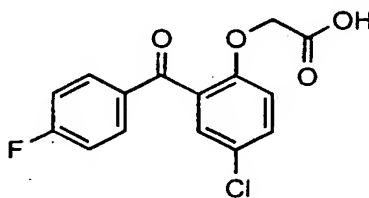
59

4-Fluorobenzoyl chloride (3.2 mL, 27.08 mmol), 4-chloroanisole (3.98 g, 27.91 mmol), aluminum chloride (5.78 g, 43.34 mmol) and dichloromethane (120 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/ethyl acetate to provide **59** as a yellow solid (3.48 g, 51%).

Step B:

60

Phenol **59** (3.48 g, 13.88 mmol), ethyl bromoacetate (1.7 mL, 15.32 mmol), K_2CO_3 (7.74 g, 56.0 mmol) and acetone were used according to general procedure II to provide **60** as a white solid, which was washed with several portions of ether, dried in vacuo and used in subsequent reactions without any further purification.

Step C:

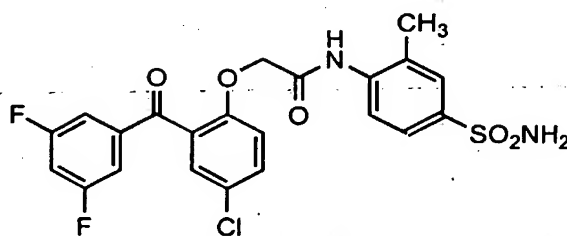
61

Ester 60 (4.7 g, 13.9 mmol), lithium hydroxide (1.45 g, 34.56 mmol), water (20 mL), THF (40 mL) and EtOH (20 mL) were used according to general procedure III to afford 61 as a viscous, clear oil. Ether was added to the oil causing a white solid to form, which was filtered and dried to provide 61 as a white solid, which was used without any further purification.

Step D:

Carboxylic acid 61 (0.237 g, 0.786 mmol), sulfoxide 399 (0.198 g, 0.88 mmol), EDAC (0.285 g, 1.49 mmol), HOBt (0.131 g, 0.97 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH₂Cl₂/CH₃OH as eluant to provide 58 as a tan solid (0.280 g, 71%). ¹H NMR (DMSO-d₆, 300 MHz) δ 8.95 (s, 1H), 7.90 (m, 2H), 7.66 (dd, J= 9, 3 Hz, 1H), 7.49 (d, J= 3 Hz, 1H), 7.36 (t, J= 6 Hz, 2H), 7.26 (d, J= 9 Hz, 1H), 7.14 (d, J= 9 Hz, 1H), 6.84 (m, 2H), 4.73 (s, 2H), 3.75 (m, 2H), 3.58 (m, 2H), 2.91 (m, 2H), 2.71 (m, 2H), 2.03 (s, 3H).

Example 22

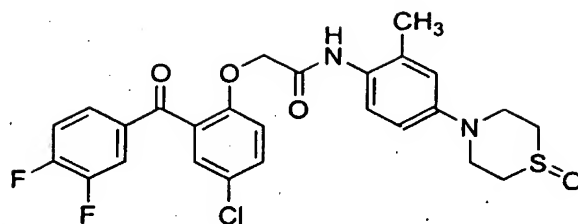


62

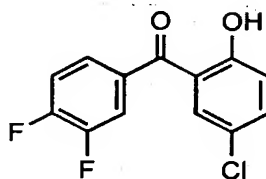
Carboxylic acid 49 (0.123 g, 0.377 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (2 drops) and chloroform (5 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, sulfonamide 466 (0.07 g, 0.37 mmol), NaHCO₃ (0.13 g, 1.55 mmol), water (1 mL) and acetone (5 mL) were used according to general procedure VI to afford 62 as a tan solid (0.07 g, 40%). ¹H NMR (DMSO-d₆, 300 MHz) δ 9.46 (s, 1H), 7.68-7.45 (m, 8H), 7.28 (m, 3H), 4.85 (s, 2H), 2.21 (s, 3H).

Example 23

104

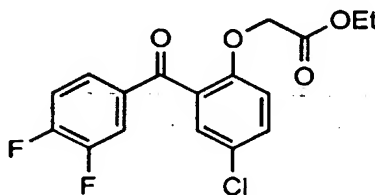


63

Step A:

64

3,4-Difluorobenzoyl chloride (5.01 g, 28.37 mmol), 4-chloroanisole (4.04 g, 28.33 mmol), aluminum chloride (5.61 g, 42.07 mmol) and dichloromethane (100 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/ethyl acetate as eluant to provide **64** as a yellow solid (2.65 g, 35%). ¹H NMR (CDCl₃, 300 MHz) δ 11.64 (s, 1H), 7.64-7.30 (m, 5H), 7.09 (d, J= 9 Hz, 1H).

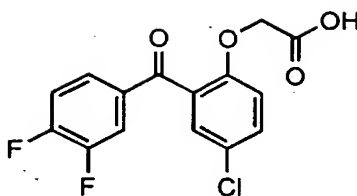
Step B:

65

Phenol **64** (2.65 g, 9.86 mmol), ethyl bromoacetate (1.20 mL, 10.82 mmol), K₂CO₃ (5.37 g, 38.85 mmol) and acetone (35 mL) were used according to general procedure II to provide **65** as white solid (3.39 g, 96%) that was used without any further purification.

Step C:

105

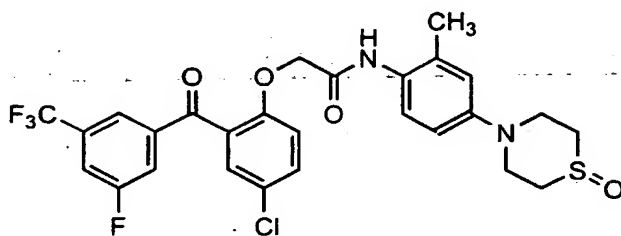


66

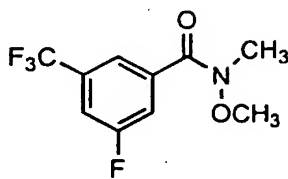
Ester **65** (3.39 g, 9.56 mmol), lithium hydroxide (0.80 g, 19.07 mmol), water (20 mL), THF (40 mL) and EtOH (20 mL) were used according to general procedure III to provide
5 **66** as a white solid which was used without any further purification.

Step D:

Carboxylic acid **66** (0.146 g, 0.447 mmol), sulfoxide **399** (0.096 g, 0.429 mmol), EDAC
10 (0.183 g, 0.955 mmol), HOBt (0.077 g, 0.569 mmol) and DMF (5 mL) were used
according to general procedure IV. The product was purified by flash chromatography
using 95:5 CH₂Cl₂/CH₃OH as eluant to provide **63** as a tan solid (0.150 g, 63%). ¹H NMR
(CDCl₃, 300 MHz) δ 8.35 (s, 1H), 7.79-7.56 (m, 3H), 7.41 (d, J = 3 Hz, 1H), 7.32 (m, 2H),
7.09 (d, J = 9 Hz, 1H), 6.87 (br s, 1H), 4.73 (s, 2H), 4.04 (m, 2H), 3.58 (m, 2H), 3.02 (m,
15 4H), 1.62 (s, 3H).

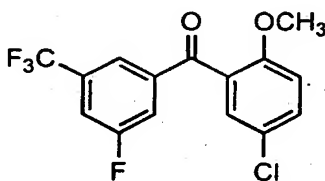
Example 24

67

Step A:

68

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed N,O-dimethylhydroxylamine hydrochloride (2.80 g, 28.7 mmol), Et₃N (9.0 mL, 64.57 mmol) and CHCl₃ (50 mL). The solution was cooled to 0 °C and 3-trifluoromethyl-5-fluorobenzoyl chloride (5.0 g, 22.07 mmol) was added dropwise over several minutes. The resulting solution was allowed to stir at 0 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 30 min. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to provide 68 as a clear oil which was used without any further purification. ¹H NMR (CDCl₃, 300 MHz) δ 7.83 (s, 1H), 7.65 (d, J= 9 Hz, 1H), 7.46 (d, J= 9 Hz, 1H), 3.59 (s, 3H), 3.42 (s, 3H).

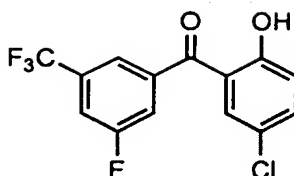
Step B:

69

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (4.05 g, 18.29 mmol) and Et₂O (75 mL). The solution was cooled to -78 °C and n-butyl lithium (13 mL of a 1.6 M solution in hexane, 20.8 mmol) was added dropwise. The resulting mixture was allowed to stir at -78 °C for 15 min, after which time amide 68 (5.04 g, 20.07 mmol) was added dropwise. The mixture was allowed to stir at -78 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 2 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure afford 69 as a yellow solid (6.14 g, 92%), which was used in subsequent reactions without any further purification. ¹H NMR (CDCl₃, 300 MHz) δ 7.84 (s, 1H), 7.68 (d, J= 9 Hz, 1H), 7.58-7.51 (m, 2H), 7.44 (d, J= 3 Hz, 1H), 7.00 (d, J= 9 Hz, 1H), 3.74 (s, 3H).

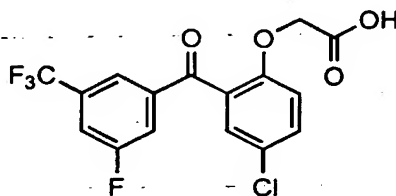
Step C:

107



70

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed **69** (6.14 g, 18.46 mmol) and CH_2Cl_2 (100 mL). The solution was cooled to -78°C and boron tribromide (50 mL of a 1.0 M solution in CH_2Cl_2 , 50 mmol) was added dropwise over several minutes. The resulting dark mixture was allowed to stir at -78°C for 30 min, after which time it was allowed to warm to rt and stir for an additional 1h. The mixture was carefully poured over ice and the two-phase mixture was stirred for 30 min. It was then poured into a separatory funnel containing CH_2Cl_2 and water. The organic layer was collected, washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to afford **70** as a yellow solid (5.68 g, 96%), which was used without any further purification. ^1H NMR (CDCl_3 , 300 MHz) δ 11.61 (s, 1H), 7.77 (s, 1H), 7.65-7.54 (m, 3H), 7.47 (d, $J = 3$ Hz, 1H), 7.12 (d, $J = 9$ Hz, 1H).

Step D:

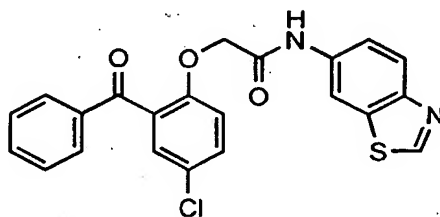
71

Phenol **70** (5.68 g, 17.83 mmol), ethyl bromoacetate (2 mL, 18.03 mmol), K_2CO_3 (9.61 g, 69.53 mmol) and acetone (35 mL) were used according to general procedure II to provide the ester as a yellow, viscous oil which was used without any further purification. The ester (6.83 g, 16.88 mmol), lithium hydroxide (1.42 g, 33.84 mmol), water (20 mL), THF (50 mL) and EtOH (20 mL) were used according to general procedure III. The product was washed with several portions of ether to provide **71** as a white solid that was used without any further purification.

Step E:

Carboxylic acid **71** (0.168 g, 0.445 mmol), sulfoxide **399** (0.098 g, 0.438 mmol), EDAC (0.211 g, 1.10 mmol), HOBt (0.076 g, 0.562 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5
5 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ as eluant to provide **67** as a white solid (0.18 g, 69%). ^1H NMR (CDCl_3 , 300 MHz) δ 8.26 (s, 1H), 7.92 (s, 1H), 7.73 (d, J = 6 Hz, 1H), 7.64-7.59 (m, 3H), 7.44 (d, J = 3 Hz, 1H), 7.10 (d, J = 9 Hz, 1H), 6.90 (m, 1H), 4.74 (s, 2H), 4.03 (m, 2H), 3.58 (m, 2H), 3.02 (m, 4H), 2.21 (s, 3H).

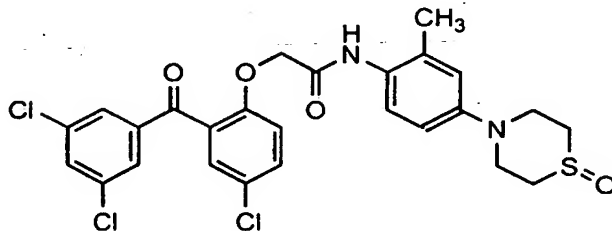
10 Example 25

**72**

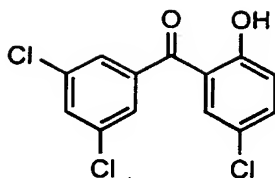
Carboxylic acid **105** (0.195 g, 0.65 mmol), 6-aminobenzthiazole (Lancaster, 0.105 g, 0.70 mmol), EDAC (0.23 g, 1.20 mmol), HOBt (0.105 g, 0.78 mmol) and DMF (5 mL) were
15 used according to general procedure IV, with the exception that no Et_3N was used. The product was purified by flash chromatography using 1:1 hexane/ethyl acetate as eluant to provide **72** as a white solid (0.24 g, 87%). ^1H NMR (CDCl_3 , 400 MHz) δ 9.51 (s, 1H), 8.92 (s, 1H), 8.64 (s, 1H), 8.08 (d, J = 8 Hz, 1H), 7.92 (d, J = 8 Hz, 1H), 7.67-7.63 (m, 2H), 7.55-7.50 (m, 3H), 7.42 (s, 1H), 7.04 (d, J = 8 Hz, 1H), 4.73 (s, 2H).

20

Example 26

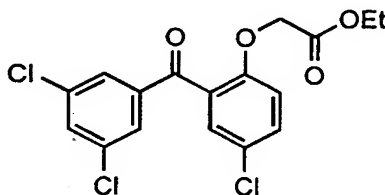
**73****Step A:**

109



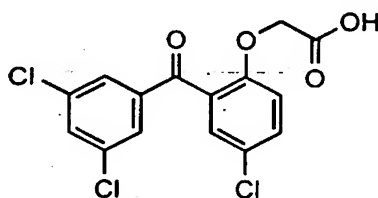
74

3,5-Dichlorobenzoyl chloride (5.0 g, 23.87 mmol), 4-chloroanisole (3.40 g, 23.84 mmol), aluminum chloride (5.56 g, 41.70 mmol) and dichloromethane (100 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/dichloromethane to provide **74** as a yellow solid (1.18 g, 16%). ¹H NMR (CDCl₃, 300 MHz) δ 11.62 (s, 1H), 7.65 (s, 1H), 7.56-7.49 (m, 4H), 7.09 (d, J = 9 Hz, 1H).

Step B:

75

Phenol **74** (1.18 g, 3.91 mmol), ethyl bromoacetate (0.6 mL, 5.41 mmol), K₂CO₃ (2.66 g, 19.25 mmol) and acetone (15 mL) were used according to general procedure II to afford **75** as a viscous, yellow oil, which was used without any further purification.

Step C:

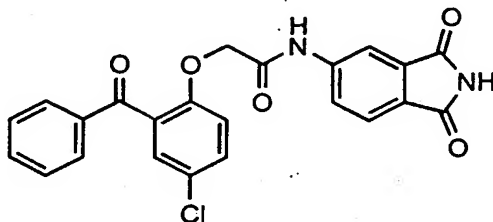
76

Ester **75** (3.9 mmol), lithium hydroxide (0.396 g, 9.44 mmol), water (10 mL), THF (40 mL) and EtOH (10 mL) were used according to general procedure III to afford **76** as a white solid, which was washed with hexane and dried in vacuo (1.32 g, 94%).

Step D:

Carboxylic acid 76 (0.128 g, 0.356 mmol), sulfoxide 399 (0.076 g, 0.339 mmol), EDAC (0.114 g, 0.595 mmol), HOBt (0.057 g, 0.422 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 chloroform/methanol as eluant to afford 73 as a white solid (0.125 g, 65%). ¹H NMR (CDCl₃, 300 MHz) δ 8.20 (s, 1H), 7.70 (s, 1H), 7.62-7.59 (m, 2H), 7.42 (d, J= 3 Hz, 1H), 7.08 (d, J= 9 Hz, 1H), 6.86 (br s, 2H), 4.72 (s, 2H), 4.04 (m, 2H), 3.62-3.55 (m, 2H), 3.06-2.92 (m, 4H), 2.21 (s, 3H).

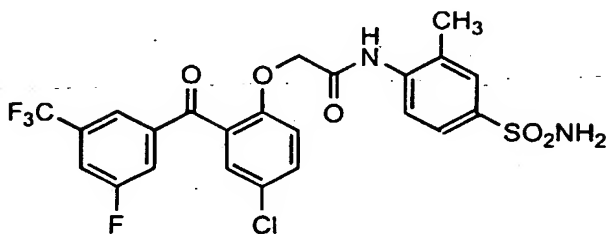
Example 27



77

Carboxylic acid 105 (0.125 g, 0.417 mmol), 3-aminophthalimide (TCI, 0.062 g, 0.382 mmol), EDAC (0.132 g, 0.689 mmol), HOBt (0.063 g, 0.467 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford 77 as a white solid (0.038 g, 22%). ¹H NMR (CDCl₃, 300 MHz) δ 10.10 (s, 1H), 8.39 (s, 1H), 8.25 (dd, J= 9, 3 Hz, 1H), 7.97 (d, J= 9 Hz, 2H), 7.80 (d, J= 9 Hz, 1H), 7.73 (t, J= 6 Hz, 1H), 7.63-7.56 (m, 4H), 7.48 (d, J= 3 Hz, 1H), 7.10 (d, J= 9 Hz, 1H), 4.82 (s, 2H).

Example 28

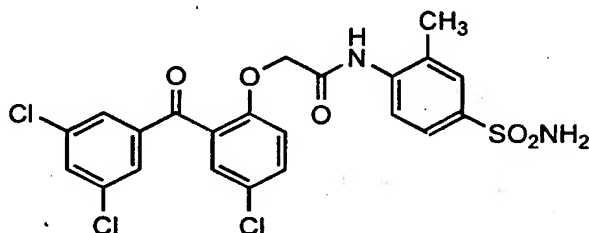


78

Carboxylic acid 71 (11.24 g, 29.84 mmol), oxalyl chloride (3.9 mL, 44.71 mmol), DMF (5 mL) and chloroform (250 mL) were used according to general procedure V to prepare the

acid chloride, which was used without further purification. The acid chloride, sulfonamide 466 (5.12 g, 27.49 mmol), NaHCO₃ (11.12 g, 132 mmol), acetone (300 mL) and water (10 mL) were used according to general procedure VI. The product was purified by crystallization from a mixture of acetonitrile/water to provide **78** as a white solid (9.01 g, 60%). ¹H NMR (DMSO-d₆, 300 MHz) δ 9.47 (s, 1H), 8.05 (d, J= 9 Hz, 1H), 7.93-7.90 (m, 2H), 7.73-7.50 (m, 5H), 7.30-7.26 (m, 3H), 4.84 (s, 2H), 2.19 (s, 3H). Anal Calcd. for C₂₃H₁₇ClF₄N₂O₅S: C, 50.70; H, 3.14; N, 5.14. Found: C, 50.75; H, 3.10; N, 5.21.

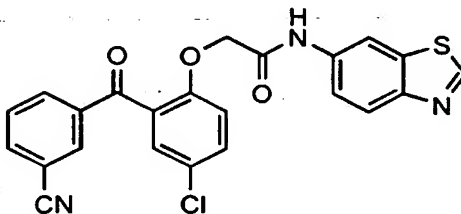
Example 29



79

Carboxylic acid **76** (0.157 g, 0.437 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (3 drops) and dichloromethane (5 mL) were used according to general procedure V to prepare the acid chloride, which was used without any further purification. The acid chloride, sulfonamide 466 (0.072 g, 0.387 mmol), NaHCO₃ (0.210 g, 2.5 mmol), acetone (5 mL) and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **79** as a white solid (0.117 g, 57%). ¹H NMR (DMSO-d₆, 300 MHz) δ 9.45 (s, 1H), 7.94 (s, 1H), 7.76 (s, 2H), 7.75-7.55 (m, 5H), 7.30-7.25 (m, 3H), 4.85 (s, 2H), 2.22 (s, 3H).

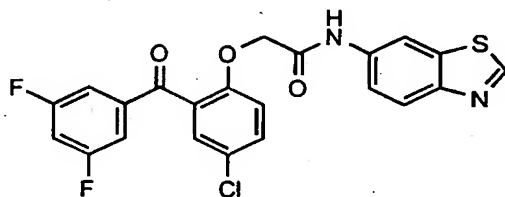
Example 30



80

Carboxylic acid **131** (0.109 g, 0.345 mmol), 6-aminobenzthiazole (Lancaster, 0.056 g, 0.373 mmol), EDAC (0.164 g, 0.855 mmol), HOBt (0.064 g, 0.474 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **80** as a white solid (0.120 g, 77%). ¹H NMR (DMSO-d₆, 300 MHz) δ 10.18 (s, 1H), 9.30 (s, 1H), 8.50 (s, 1H), 8.26 (s, 1H), 8.13 (d, J = 9 Hz, 1H), 8.05 (t, J = 9 Hz, 2H), 7.75-7.66 (m, 2H), 7.56 (m, 2H), 7.26 (d, J = 9 Hz, 1H), 4.81 (s, 2H).

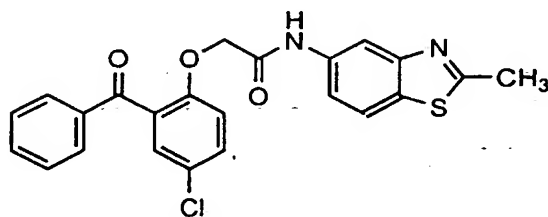
Example 31



81

Carboxylic acid **49** (0.106 g, 0.324 mmol), 6-aminobenzthiazole (Lancaster, 0.051 g, 0.3393 mmol), EDAC (0.158 g, 0.824 mmol), HOBt (0.0584 g, 0.429 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **81** as a white solid (0.105 g, 70%). ¹H NMR (DMSO-d₆, 300 MHz) δ 10.22 (s, 1H), 9.31 (s, 1H), 8.48 (d, J = 3 Hz, 1H), 8.04 (d, J = 9 Hz, 1H), 7.67 (dd, J = 9, 3 Hz, 1H), 7.59-7.48 (m, 5H), 7.25 (d, J = 9 Hz, 1H), 4.82 (s, 2H).

Example 32

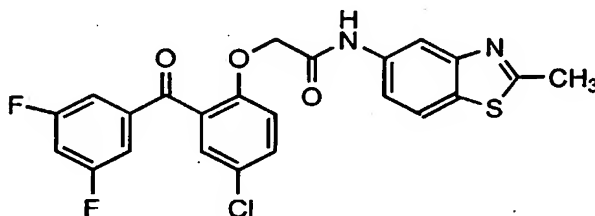


82

Carboxylic acid **105** (0.129 g, 0.43 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (3 mL) were used to prepare the acid chloride according to

general procedure V. The acid chloride, 5-amino-2-methylbenzthiazole dihydrochloride (0.087 g, 0.367 mmol), NaHCO_3 (0.324 g, 3.86 mmol), water (0.5 mL) and acetone (5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford 82 as a white solid (0.118 g, 74%). ^1H NMR (DMSO-d_6 , 300 MHz) δ 10.02 (s, 1H), 8.20 (d, $J = 3$ Hz, 1H), 7.95 (d, $J = 9$ Hz, 1H), 7.85 (d, $J = 9$ Hz, 2H), 7.66-7.47 (m, 6H), 7.26 (d, $J = 9$ Hz, 1H), 4.78 (s, 2H), 2.80 (s, 3H).

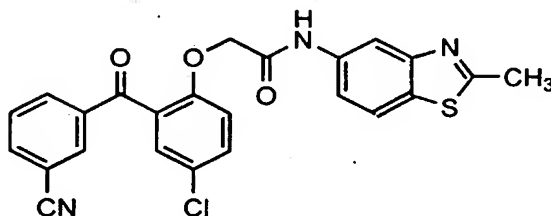
Example 33



83

Carboxylic acid 49 (0.110 g, 0.337 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (5 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, 5-amino-2-methylbenzthiazole dihydrochloride (0.078 g, 0.329 mmol), NaHCO_3 (0.293 g, 3.49 mmol), water (0.5 mL) and acetone (5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford 83 as a white solid (0.079 g, 49%). ^1H NMR (DMSO-d_6 , 300 MHz) δ 10.12 (s, 1H), 8.22 (s, 1H), 7.95 (d, $J = 9$ Hz, 1H), 7.67 (dd, $J = 9, 3$ Hz, 1H), 7.58-7.48 (m, 5H), 7.25 (d, $J = 9$ Hz, 1H), 4.81 (s, 2H), 2.80 (s, 3H).

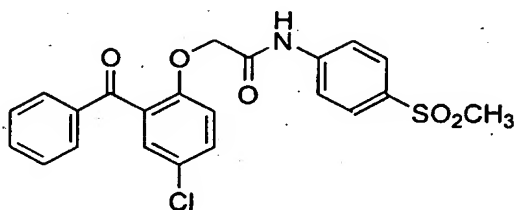
Example 34



84

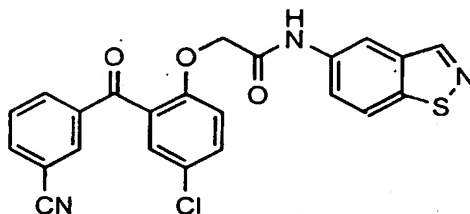
Carboxylic acid **129** (0.094 g, 0.298 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (5 mL) were used to prepared the acid chloride according to general procedure V. The acid chloride, 5-amino-2-methylbenzthiazole dihydrochloride (0.068 g, 0.287 mmol), NaHCO₃ (0.310 g, 3.69 mmol), water (0.5 mL) and acetone (5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **84** as a tan solid (0.042 g, 31%). ¹H NMR (DMSO-d₆, 300 MHz) δ 10.09 (s, 1H), 8.22 (d, J= 9 Hz, 2H), 8.13 (d, J= 6Hz, 1H), 8.06 (d, J= 9 Hz, 1H), 7.94 (d, J= 9 Hz, 1H), 7.75-7.66 (m, 2H), 7.55 (d, J= 3 Hz, 1H), 7.49 (d, J= 3 Hz, 1H), 7.25 (d, J= 6 Hz, 1H), 4.78 (s, 2H), 2.80 (s, 3H).

Example 35

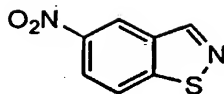
**85**

Carboxylic acid **105** (0.104 g, 0.347 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (4 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, 4-methylsulfonylaniline (0.06 g, 0.350 mmol), NaHCO₃ (0.214 g, 2.55 mmol), water (0.5 mL) and acetone (6 mL) were used according to general procedure VI. The product was purified by flash chromatography using 3:2 ethyl acetate/hexane to afford **85** as a white solid (0.061 g, 40%). ¹H NMR (DMSO-d₆, 300 MHz) δ 10.34 (s, 1H), 7.90-7.76 (m, 6H), 7.66-7.47 (m, 5H), 7.22 (d, J= 9 Hz, 1H), 3.18 (s, 3H).

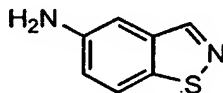
Example 36

**86**

115

Step A:**87**

Into a stirred Parr bomb were placed 2-chloro-5-nitrobenzaldehyde (1.84 g, 9.92 mmol), sulfur (0.360 g, 11.23 mmol), ammonia (5 mL) and methanol (30 mL). The bomb was sealed and was heated, with stirring, to 85-90 °C for 16 h. The mixture was allowed to cool to rt and was poured into a separatory funnel containing dichloromethane and water. The organic layer was collected, washed with water, brine, dried over MgSO₄, filtered and the solvents were removed to afford **87** as an orange solid (1.26 g, 70%). ¹H NMR (DMSO-d₆, 400 MHz) δ 9.33 (s, 1H), 9.13 (d, J= 4 Hz, 1H), 8.47 (d, J= 12 Hz, 1H), 8.36 (dd, J= 12, 4 Hz, 1H).

Step B:**88**

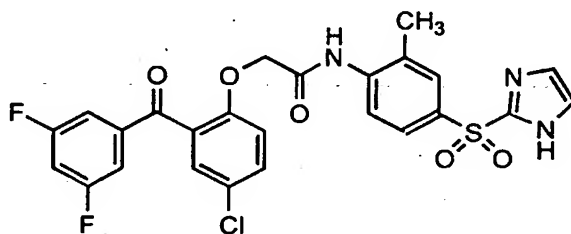
Compound **87** (1.26 g, 6.97 mmol), iron powder (1.89 g, 33.84 mmol), concentrated hydrochloric acid (7 mL) and ethanol (35 mL) were added to a round-bottom flask. The mixture was heated to reflux and stirred for 2 h, after which time it was allowed to cool to rt. The mixture was then poured into water and was made basic by the slow addition of solid NaHCO₃. It was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected, washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to afford **88** as a tan solid (0.470 g, 45%). ¹H NMR (DMSO-d₆, 400 MHz) δ 8.82 (s, 1H), 7.81 (d, J= 9 Hz, 1H), 7.20 (d, J= 3 Hz, 1H), 6.99 (dd, J= 9, 3 Hz, 1H), 5.40 (s, 2H).

Step C:

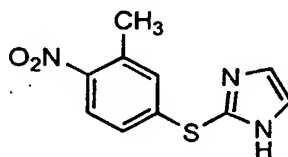
Carboxylic acid **129** (0.125 g, 0.396 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (5 mL) were used to prepare the acid chloride according to

general procedure V. The acid chloride, amine **88** (0.063 g, 0.419 mmol), NaHCO_3 (0.173 g, 2.06 mmol), water (0.5 mL) and acetone (5 mL) were used according to general procedure VI to afford a yellow solid. The solid was washed with several portions of ether and was dried in vacuo to provide **86** as a yellow solid (0.083 g, 47%).

Example 37

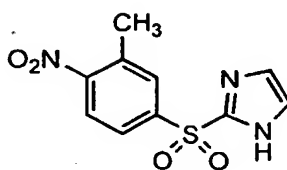
**89**

Step A:

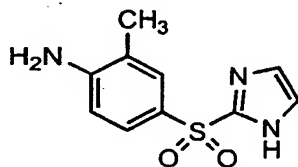
**90**

Into a round-bottom flask were placed 5-fluoro-2-nitrotoluene (Lancaster, 2.03 g, 13.09 mmol), 2-thioimidazole (1.54 g, 15.38 mmol), K_2CO_3 (6.31 g, 45.66 mmol) and DMF (25 mL). The resulting mixture was heated to 80-90 °C for 3 h and was then allowed to cool to 50 °C and stir overnight. The mixture was allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to afford **90** as an orange oil which was used without purification. ^1H NMR (CDCl_3 , 300 MHz) δ 7.85 (d, J = 9 Hz, 1H), 7.80-7.30 (br m, 2H), 7.08 (s, 1H), 7.03 (d, J = 6 Hz, 1H), 2.53 (s, 3H).

Step B:

**91**

Into a round-bottom flask were placed compound **90** (0.121 g, 0.51 mmol), glacial acetic acid (3 mL) and hydrogen peroxide (0.491 g of a 30% w/w solution, 4.33 mmol). The resulting mixture was heated to 85-90 °C for 2 h, after which time it was allowed to cool to rt and was poured into a flask containing a saturated solution of sodium bisulfite. The pH of the mixture was adjusted to pH 7 by the slow addition of solid NaHCO₃ and was then poured into a separatory funnel containing ethyl acetate. The organic layer was collected, washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to afford **91** as a white solid (0.092 g, 67%). ¹H NMR (DMSO-d₆, 400 MHz) δ 8.16 (d, J= 8 Hz, 1H), 8.04 (s, 1H), 7.93 (d, J= 8 Hz, 1H), 7.35-7.32 (br m, 2H), 2.47 (s, 3H).

Step C:**92**

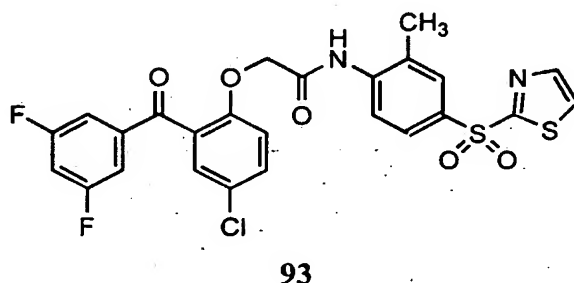
Into a Parr bottle were placed compound **91** (0.092 g, 0.34 mmol), Pd/C (0.01 g, 10% w/w), and ethanol. The bottle was purged with hydrogen (3X) and was finally pressurized to 40 psig. The mixture was allowed to stir at rt for 30 min, after which time the bottle was depressurized and the mixture was filtered through a pad of celite and the solvents were removed under reduced pressure to afford **92** as a yellowish solid (0.083 g, >100% yield), which was used without any further purification. ¹H NMR (DMSO-d₆, 400 MHz) δ 13.54 (br s, 1H), 8.77 (s, 1H), 8.74 (s, 1H), 7.60 (dd, J= 8, 4 Hz, 1H), 7.45 (d, J= 4 Hz, 1H), 7.18 (br s, 2H), 7.09 (d, J= 8 Hz, 1H), 2.05 (s, 3H).

Step D:

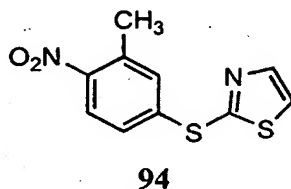
Carboxylic acid **49** (0.100 g, 0.31 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and chloroform (3 mL) were used to prepared the acid chloride according to general procedure V. The acid chloride, amine **92** (0.065 g, 0.273 mmol), NaHCO₃ (0.134 g, 1.59 mmol), water (0.5 mL) and acetone (4 mL) were used according to general procedure VI to afford a tan solid. The solid was washed with several portions of ether and

dried to afford **89** as a tan solid (0.105 g, 62%). ¹H NMR (DMSO-d₆, 300 MHz) δ 13.74 (s, 1H), 10.26 (s, 1H), 7.70-7.27 (m, 10H), 6.95 (d, J = 9 Hz, 1H), 5.19 (s, 2H), 2.20 (s, 3H).

5 **Example 38**

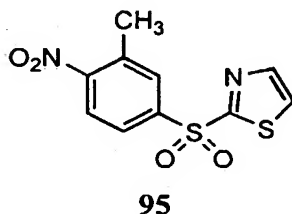


Step A:

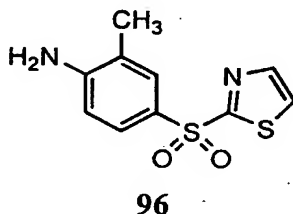


10 Into a round-bottom flask were placed 5-fluoro-2-nitrotoluene (Lancaster, 1.65 g, 13.09 mmol), 2-thiothiazole (1.46 g, 12.46 mmol), K₂CO₃ (5.04 g, 36.47 mmol) and DMF (25 mL). The resulting mixture was heated to 80-90 °C for 3 h and was then allowed to cool to 50 °C and stir overnight. The mixture was allowed to cool to rt and was poured into a
15 separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to afford **94** (2.51 g, 93%) as an orange solid which was used without purification. ¹H NMR (CDCl₃, 400 MHz) δ 7.94 (d, J = 8 Hz, 1H), 7.87 (d, J = 4 Hz, 1H), 7.44 (d, J = 4 Hz, 1H), 7.38-7.34 (m, 2H), 2.57 (s, 3H).

20 **Step B:**



Into a round-bottom flask were placed compound 94 (0.103 g, 0.41 mmol), glacial acetic acid (3 mL) and hydrogen peroxide (0.210 g of a 30% w/w solution, 1.85 mmol). The resulting mixture was heated to 85-90 °C for 2 h, after which time it was allowed to cool to rt and was poured into a flask containing a saturated solution of sodium bisulfite. The pH of the mixture was adjusted to pH 7 by the slow addition of solid NaHCO₃ and was then poured into a separatory funnel containing ethyl acetate. The organic layer was collected, washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to afford 95 as a white solid (0.103 g, 89%). ¹H NMR (CDCl₃, 400 MHz) δ 8.10-8.00 (m, 4H), 7.73 (d, J= 4 Hz, 1H), 2.64 (s, 3H).

Step C:

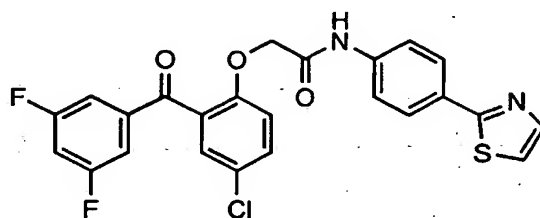
Into a Parr bottle were placed compound 95 (0.074 g, 0.34 mmol), Pd/C (0.018 g, 10% w/w), and ethanol (2 mL). The bottle was purged with hydrogen (3X) and was finally pressurized to 45 psig. The mixture was allowed to stir at rt for 30 min, after which time the bottle was depressurized and the mixture was filtered through a pad of celite and the solvents were removed under reduced pressure to afford 96 as a yellow oil, which was used without any further purification. ¹H NMR (CDCl₃, 300 MHz) δ 7.94 (d, J= 3 Hz, 1H), 7.87 (d, J= 9 Hz, 1H), 7.74 (s, 1H), 7.65 (d, J= 3 Hz, 1H), 7.31 (d, J= 9 Hz, 1H), 5.81 (br s, 2H), 2.13 (s, 3H).

Step D:

Carboxylic acid 49 (0.104 g, 0.31 mmol), oxalyl chloride (0.6 mL of a 2.0 M solution in dichloromethane, 1.2 mmol), DMF (4 drops) and chloroform (4 mL) were used to prepared the acid chloride according to general procedure V. The acid chloride, amine 96 (0.071 g, 0.2793 mmol), NaHCO₃ (0.1434 g, 1.70 mmol), water (0.5 mL) and acetone (4 mL) were used according to general procedure VI to afford a tan solid. The solid was washed with several portions of ether and dried to afford 93 as a tan solid (0.129 g, 82%).

^1H NMR (DMSO- d_6 , 300 MHz) δ 10.35 (s, 1H), 8.25 (d, J = 3 Hz, 1H), 8.09 (d, J = 3 Hz, 1H), 7.75-7.39 (m, 7H), 7.28 (d, J = 9 Hz, 1H), 6.97 (d, J = 9 Hz, 1H), 5.20 (s, 2H), 2.22 (s, 3H).

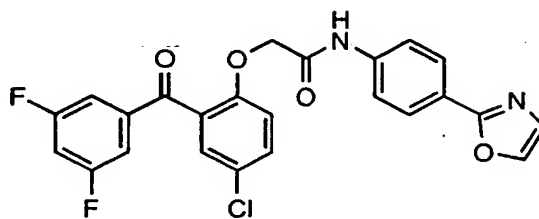
5 Example 39



97

Carboxylic acid 49 (0.108 g, 0.331 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and chloroform (3 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, the aniline (prepared according to the method of Erlenmeyer, *Helv. Chim. Acta*, 30, 2058-2060, 1947), 0.056 g, 0.318 mmol), NaHCO_3 (0.146 g, 1.74 mmol), water (0.5 mL) and acetone (6 mL) were used according to general procedure VI to provide 97 as a yellow solid (0.05 g, 32%). ^1H NMR (DMSO- d_6 , 300 MHz) δ 10.19 (s, 1H), 7.95-7.90 (m, 3H), 7.76 (d, J = 3 Hz, 1H), 7.70-7.48 (m, 7H), 7.23 (d, J = 9 Hz, 1H), 4.80 (s, 2H).

Example 40

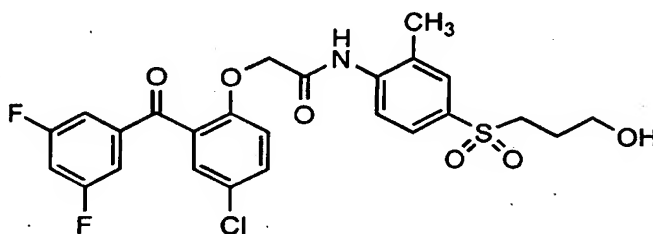


98

Carboxylic acid 49 (0.112 g, 0.343 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and chloroform (3 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, the aniline (prepared according to the method of Brown, E.V., *Journal of Organic Chemistry*, 42(19), 3208-3209, 1977), 0.050 g, 0.312 mmol), NaHCO_3 (0.137 g, 1.63 mmol), water (0.5 mL) and acetone (6 mL) were used according to general procedure VI to provide 98 as a yellow solid (0.064 g, 44%). ^1H NMR (DMSO-

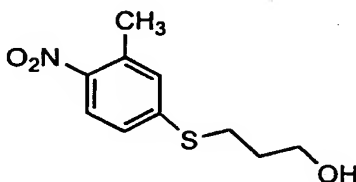
d_6 , 300 MHz) δ 10.22 (s, 1H), 8.20 (s, 1H), 7.95 (d, $J = 9$ Hz, 1H), 7.72 (d, $J = 9$ Hz, 1H), 7.69-7.47 (m, 7H), 7.37 (s, 1H), 7.23 (d, $J = 9$ Hz, 1H), 4.81 (s, 2H).

Example 41



99

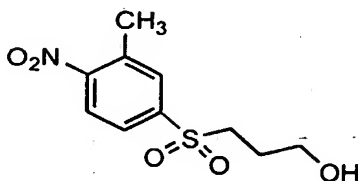
Step A:



100

Into a round-bottom flask were placed 5-fluoro-2-nitrotoluene (5.0 g, 32.2 mmol), K_2CO_3 (15.34 g, 111 mmol), 3-mercaptoethanol (3.2 mL, 37 mmol) and DMF (30 mL). The resulting mixture was allowed to stir at rt for 16 h, after which time it was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **100** as thick, yellow oil, which was used without any further purification.

Step B:



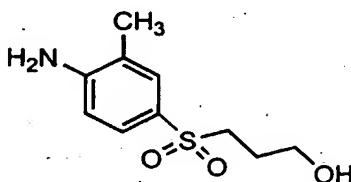
101

Into a round-bottom flask were placed compound **100** (~32 mmol), and methanol (100 mL). Into a separate flask were placed oxone (Aldrich, 29.43 g, 47.9 mmol) and water (125 mL). The oxone solution was added dropwise over several minutes to the solution of compound **100** at rt. The resulting solution was allowed to stir at rt for 1 h. It was then

122

poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and washed with water, brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to afford a yellow oil, which was dried in vacuo to provide **101** as a yellow solid (7.91 g, 95%).

5 **Step C:**



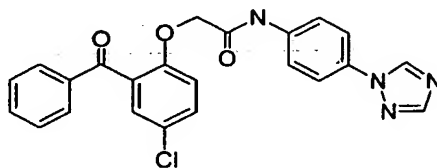
102

Into a Parr bottle were placed compound **101** (0.522 g, 2.01 mmol), Pd/C (0.04 g, 10% w/w) and EtOH (5 mL). The bottle was purged with hydrogen (3X) and was finally
10 pressurized with hydrogen to 40 psig. The resulting mixture was allowed to stir at rt for 1 h, after which time it was filtered through a pad of celite, and the solvents were removed under reduced pressure to afford a green oil which solidified in vacuo to afford **102** as a yellowish solid (0.44 g, 95%).

15 **Step D:**

Carboxylic acid **49** (0.302 g, 0.924 mmol), oxalyl chloride (0.15 mL, 1.72 mmol), DMF (4 drops) and chloroform (10 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, amine **102** (0.190 g, 0.86 mmol), NaHCO_3 (0.323 g, 4.16 mmol), water (0.5 mL) and acetone (10 mL) were used according to general
20 procedure X to provide **99** as a tan solid (0.326 g, 70%).

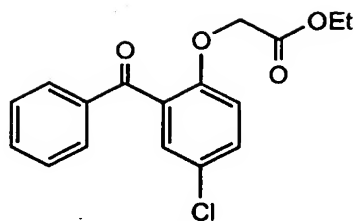
Example 43:



103

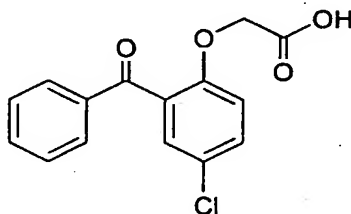
25 **Step A:**

123



104

This reaction was run according to general procedure II using 5-chloro-2-hydroxybenzophenone (15 g, 64 mmol), ethyl bromoacetate (7.7 mL, 71 mmol) and potassium carbonate and (44 g, 320 mmol). A 96% yield of **104** was obtained as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 1.8 (t, 3H), 4.1 (q, 2H), 4.8 (s, 2H), 7-7.8 (m, 8H).

Step B:

105

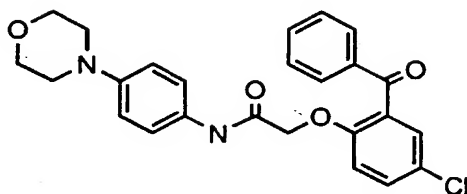
This reaction was run according to general procedure III using **104** (19.6 g, 62 mmol) and LiOH.H₂O (3.18 g, 76 mmol) in ethanol (250 mL) and water (70 mL) stirred for 1 h at rt. After extraction with methylene chloride, drying (MgSO₄) and solvent removal, an 86% yield of **105** was obtained as white foam. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.6 (s, 2H), 7-7.8 (m, 8H), 13 (s, 1H).

Step C:

A mixture of **105** (1 g, 3.4 mmol) and 18 mL of thionyl chloride was refluxed for 1 h. Concentration of the reaction mixture resulted in a crude product that was dissolved in acetonitrile. This was added dropwise to a stirred mixture of 1-(4'-aminophenyl)-1,2,4-triazole (0.54 g, 3.4 mmol) and triethylamine (0.73 mL, 5.25 mmol) in acetonitrile (10 mL). The mixture was refluxed for 6 h and stirred at rt for 24 h. Ethyl acetate was added to the reaction mixture. After washing with water, drying (MgSO₄) and solvent removal, the crude product was purified by flash column chromatography on silica with 4% methanol in methylene chloride as the eluent. This gave 0.039 g (3%) of **103** as a white

solid. ^1H NMR (DMSO- d_6 , 300 MHz) δ 4.7 (s, 2H), 7.2-7.8 (m, 12H), 8.2 (s, 1H), 9.2 (s, 1H), 10.0 (s, 1H).

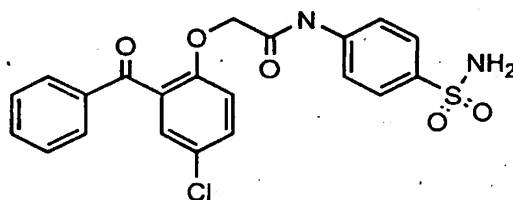
Example 44:



106

Following the procedure described for the synthesis of 103 and using 4-morpholinoaniline, a 38% yield of 106 was obtained as a gray solid. ^1H NMR (DMSO- d_6 , 300 MHz) δ 3 (s, 4H), 3.7 (s, 4H), 4.6 (s, 2H), 6.82 (m, 2H), 7.1-7.8 (m, 10H), 9.4 (s, 1H).

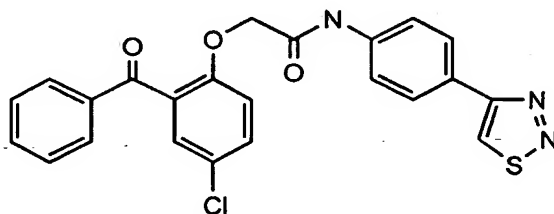
Example 45:



107

Following the procedure described for the synthesis of 103 and using sulfanilamide, a 6% yield of 107 was obtained as a white solid after purification by flash column chromatography on silica gel with 20% acetone in methylene chloride. ^1H NMR (DMSO- d_6 , 300 MHz) δ 4.7 (s, 2H), 6.82 (m, 2H), 7.1-7.8 (m, 12H), 10.1 (s, 1H).

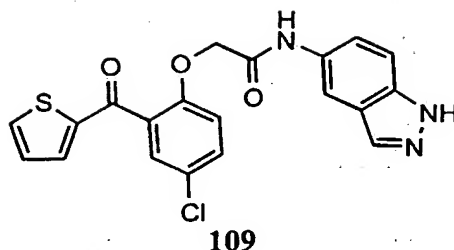
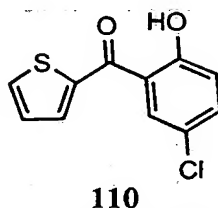
Example 46:



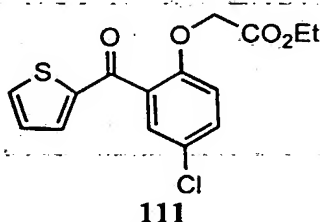
108

Following the procedure described for the synthesis of 103 and using 4-(4-aminophenyl)-1,2,3-thiadiazole as the aniline, a 20% yield of 108 was obtained as a gray solid. ^1H NMR (DMSO- d_6 , 300 MHz) δ 4.7 (s, 2H), 7.2 (d, 1H), 7.4-8.1 (m, 112H), 9.41 (s, 1H), 10.0 (s, 1H).

125

Example 47:**Step A:**

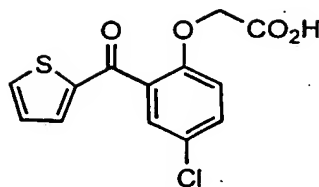
This reaction was run according to general procedure I with 2-thiophenecarbonyl chloride (1.5 mL, 14 mmol), p-chloroanisole (1.7 mL, 14 mmol) and aluminum chloride (1.9 g, 14 mmol) were refluxed in methylene chloride (200 mL) for 24 h. A 39% yield of **110** was obtained after purification by flash column chromatography on silica gel with methylene chloride/hexane (1:1). ¹H NMR (DMSO-d₆, 300 MHz) δ 6.95 (d, 1H), 7.19 (t, 1H), 7.32 (d, 1H), 7.38 (dd, 1H), 7.51 (d, 1H), 8.06 (d, 1H), 10.3 (s, 1H).

Step B:

This reaction was run according to general procedure II using **110** (0.5 g, 2.17 mmol), ethyl bromoacetate (0.24 mL, 2.17 mmol) and potassium carbonate (1.53 g, 10.85 mmol), in acetone (25 mL) for 3 h. A 97% yield of **111** was obtained as oil after workup. ¹H NMR (DMSO-d₆, 300 MHz) δ 1.1 (t, 3H), 4.1 (q, 2H), 4.8 (s, 2H), 7.07 (d, 1H), 7.19 (t, 1H), 7.43 (d, 1H), 7.49-7.52 (m, 2H), 8.07 (d, 1H).

Step C:

126

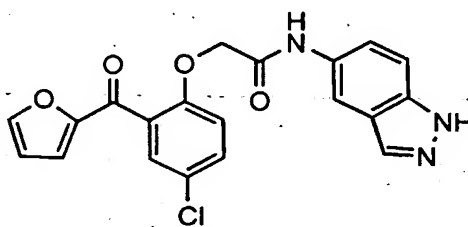


112

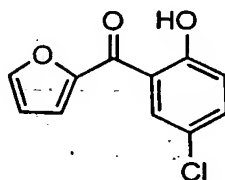
Following the procedure described in general procedure III, a 22% yield of 112 was obtained as a solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.7 (s, 2H), 7.05 (d, 1H), 7.18 (t, 1H), 7.41 (d, 1H), 7.42-7.6 (m, 2H), 8.06 (d, 1H).

Step D:

This reaction was run according to general procedure IV using 112 (0.14 g, 0.43 mmol), HOBT (0.06 g, 0.43 mmol), 5-aminoindazole (0.06 g, 0.43 mmol), EDAC (0.08 g, 0.43 mmol) and triethylamine (0.12 mL, 0.86 mmol). A 23% yield of 109 was obtained after purification by flash column chromatography on silica gel with 5% methanol in methylene chloride. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.8 (s, 2H), 7.1-7.3 (m, 2H), 7.32 (d, 1H), 7.46 (d, 1H), 7.48 (s, 1H), 7.56 (d, 1H), 7.7 (d, 1H), 7.98 (s, 1H), 8.04 (s, 1H), 8.1 (d, 1H), 9.8 (s, 1H), 13 (s, 1H).

Example 48:

113

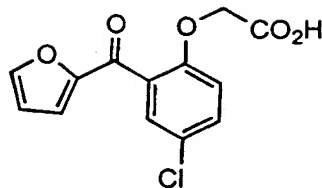
Step A:

114

Following the procedure described in general procedure I using 2-furoyl chloride and p-chloroanisole, a 73% yield of 114 was obtained as a yellow solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 6.7 (m, 1H), 6.93 (d, 1H), 7.2 (2, 1H), 7.4 (m, 2H), 8.04 (s, 1H), 10.4 (1H).

Step B:

127

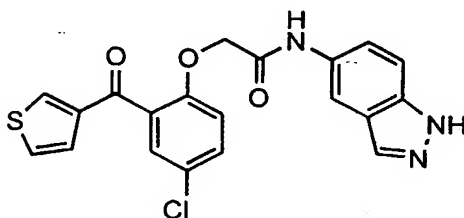


115

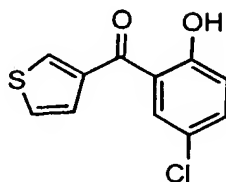
A mixture of **114** (1 g, 4.49 mmol), ethyl bromoacetate (0.5 mL, 4.49 mmol) and potassium carbonate (3.17 g, 22.45 mmol) was stirred in acetone (50 mL) for 24 h. To this was added 1N NaOH until the solid dissolved. This NaOH solution was extracted once with ethyl acetate and was then acidified with 1N HCl. This was followed by extraction with ethyl acetate. After drying (MgSO₄) and solvent removal in vacuo, the crude product was re-crystallized with hexane/ethyl acetate. Compound **115** (1 g, 79%) was collected as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.8 (s, 2H), 6.7 (m, 1H), 7.1 (d, 1H), 7.2 (d, 1H), 7.5 (m, 1H), 7.6 (d, 1H), 8.1 (s 1H), 13.1 (br s, 1H).

Step C:

Following the procedure described in general procedure IV using 5-indazole, a 61% yield of **113** was obtained as a solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.8 (s, 2H), 6.8 (m, 1H), 7.21 (d, 1H), 7.3-7.7 (m, 5H), 8.06 (s, 1H), 8.1 (s, 2H), 10 (s, 1H), 13 (s, 1H).

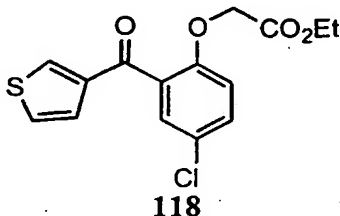
Example 49:

116

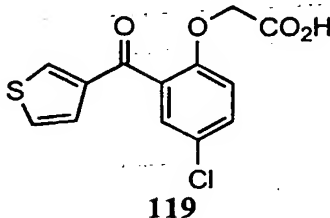
Step A:

117

A mixture of 3-thiophenecarboxyl in acid (3.58 g, 28 mmol) and thionyl chloride (15 mL) was refluxed for 3 h. The reaction mixture was concentrated and further dried in vacuo. The resultant concentrate was added to a suspension of aluminum chloride (7.61 g, 56 mmol) and p-chloroanisole (3.41 mL, 28 mmol). The suspension was heated to reflux for 24 h. Water was slowly added to the reaction mixture and this aqueous mixture was extracted with first methylene chloride, then ethyl acetate. The organic solutions were combined and dried over MgSO₄. After solvent removal, the crude product was purified by flash column chromatography on silica gel with methylene chloride/hexane (1:1). This gave 0.13 g (2%) of 117 as oil. ¹H NMR (DMSO-d₆, 300 MHz) δ 7 (d, 1H), 7.3-7.5 (m, 3H), 7.6-7.7 (m, 1H), 8.2 (m, 1H), 10.4 (s, 1H).

Step B:

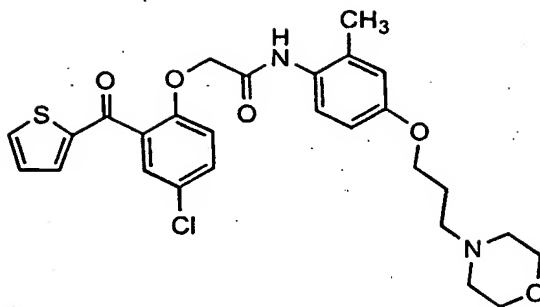
Following general procedure II, a 45% yield of 118 was obtained as oil. ¹H NMR (DMSO-d₆, 300 MHz) δ 1.1 (t, 3H), 4.08 (q, 2H), 4.8 (s, 2H), 7.07 (d, 1H), 7.38 (d, 1H), 7.44 (d, 1H), 7.49 (dd, 1H), 7.6 (dd, 1H), 8.11 (d, 1H).

Step C:

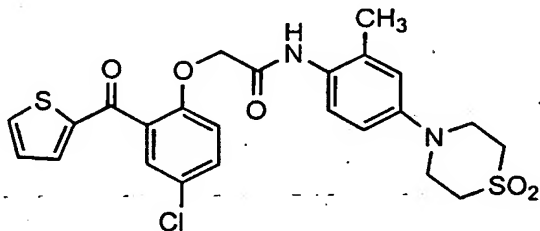
Following general procedure III, a 67% yield of 119 was obtained as oil. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.7 (s, 2H), 7.1 (d, 1H), 7.38 (d, 1H), 7.5-7.6 (m, 2H), 7.6-7.7 (m, 1H), 8.2 (m, 1H).

Step D:

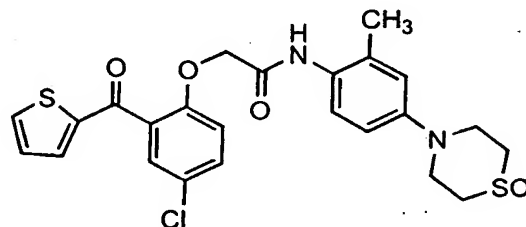
Following general procedure IV using 5-indazole, a 36% yield of 116 was obtained as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.8 (s, 2H), 7.2 (d, 1H), 7.35 (d with fine splittings, 1H), 7.42 (d, 1H), 7.45 (d, 1H), 7.5-7.6 (m, 2H), 7.6-7.65 (m, 1H), 8 (s, 1H), 8.05 (s, 1H), 8.3 (m, 1H), 9.8 (s, 1H), 13 (s, 1H).

Example 50:**120**

Following general procedure IV using 4-(3-morpholino)propyloxy-2-methylaniline, a 7% yield of **120** was obtained as a white solid after flash column chromatography on silica gel with 20% methanol in methylene chloride. ¹H NMR (DMSO-d₆, 300 MHz) δ 1.7-1.9 (m, 2H), 2 (s, 3H), 2.2-2.4 (m, 6H), 3.5-3.6 (m, 4H), 3.9 (t, 2H), 4.75 (s, 2H), 6.7 (d, 1H), 6.74 (s, 1H), 7.1-7.3 (m, 3H), 7.5 (s, 1H), 7.6 (dd, 1H), 7.63 (d, 1H), 8.08 (d, 1H), 9 (s, 1H).

Example 51:**121**

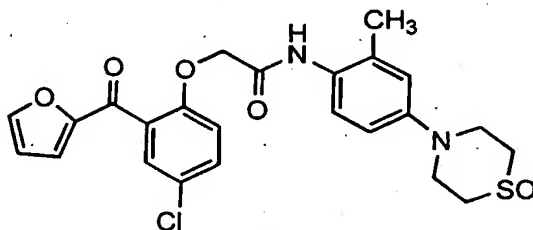
Following general procedure IV using 4-morpholinesulfonyl-2-methylaniline, a 26% yield of **121** was obtained as a white solid after flash column chromatography on silica gel with 20% methanol in methylene chloride. ¹H NMR (DMSO-d₆, 300 MHz) δ 3.1 (br s, 4H), 3.7 (s, 4H), 4.8 (s, 2H), 7 (d, 2H), 7.2-7.3 (m, 2H), 7.43 (d, 2H), 7.54 (d, 1H), 7.6 (dd, 1H), 7.7 (d, 1H), 8.2 (d, 1H), 9.8 (s, 1H).

Example 52:

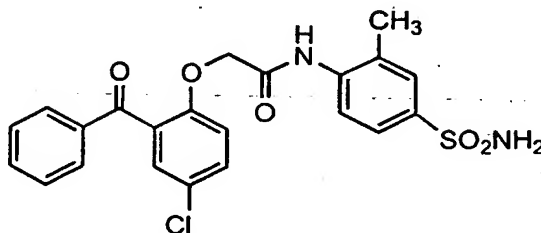
130

122

Following general procedure IV using 4-morpholinesulfonyl-2-methylaniline, a 24% yield of **122** was obtained as a white solid after flash column chromatography on silica gel with 5% methanol in methylene chloride. ¹H NMR (DMSO-d₆, 300 MHz) δ 2.6-2.8 (m, 2H), 2.9 (t, 2H), 3.5-3.6 (m, 2H), 3.7 (t, 2H), 4.8 (s, 2H), 7 (d, 2H), 7.2-7.3 (m, 2H), 7.43 (d, 2H), 7.54 (d, 1H), 7.6 (dd, 1H), 7.7 (d, 1H), 8.2 (d, 1H), 9.8 (s, 1H).

Example 53:**123**

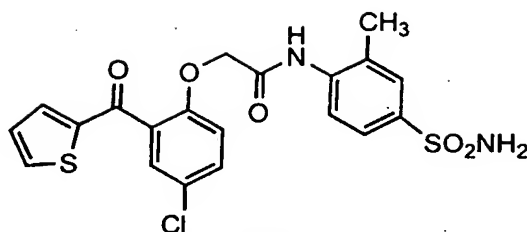
Following general procedure IV, a 35% yield of **123** was obtained as a white solid after flash column chromatography on silica gel with 3% methanol in methylene chloride. ¹H NMR (DMSO-d₆, 300 MHz) δ 2.0 (s, 3H), 2.5-2.7 (m, 2H), 2.9 (t, 2H), 3.5-3.6 (m, 2H), 3.7 (t, 2H), 4.8 (s, 2H), 6.7 (s, 1H), 6.78 (d, 1H), 6.8 (s, 1H), 7.1-7.3 (m, 2H), 7.3 (d, 1H), 7.5 (d, 1H), 7.6 (dd, 1H), 8.05 (s, 1H), 9 (s, 1H).

Example 54:**124**

Following general procedure IV, a 32% yield of **124** was obtained as a white solid after flash column chromatography on silica gel with 5% methanol in methylene chloride. ¹H NMR (DMSO-d₆, 300 MHz) δ 2.1 (s, 3H), 4.8 (s, 2H), 7.1-7.3 (m, 3H), 7.4 (s with fine splittings, 1H), 7.42-7.5 (m, 2H), 7.5-7.7 (m, 5H), 7.8 (d, 2H), 9.2 (s, 1H).

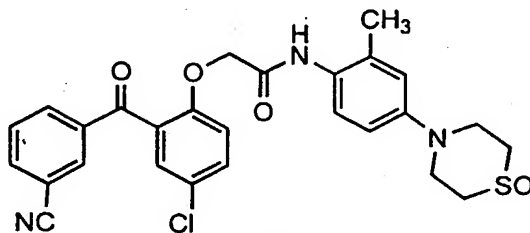
Example 55:

131

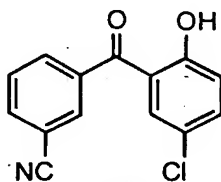


125

Following the procedure described for the synthesis of compound **103**, a 42% yield **125** was obtained as a white solid after flash column chromatography on silica gel with 3% methanol in methylene chloride. ¹H NMR (DMSO-d₆, 300 MHz) δ 2.2 (s, 3H), 4.8 (s, 2H), 7.1-7.3 (m, 3H), 7.5 (d, 1H), 7.5-7.7 (m, 5H), 7.73 (d, 1H), 8.1 (d, 1H), 9.3 (s, 1H).

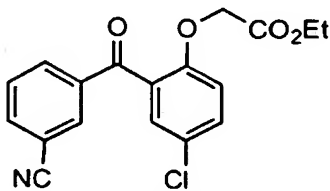
Example 56:

126

Step A:

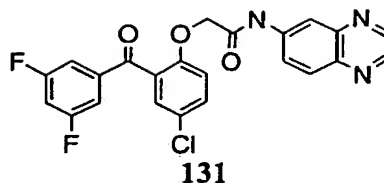
127

Following general procedure I, a 9% yield of **127** was obtained after flash column chromatography on gel with 30% hexane in methylene chloride. ¹H NMR (DMSO-d₆, 300 MHz) δ 6.97 (d, 1H), 7.38 (s, 1H), 7.42 (d, 1H), 7.7 (t, 1H), 7.98 (d, 1H), 8-8.1 (m, 2H), 10.4 (s, 1H).

Step B:

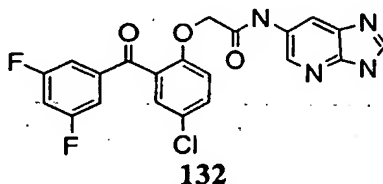
128

Acid **49** (0.1 g, 0.3 mmol), was converted to the acid chloride by reaction with oxalyl chloride (0.1 mL, 0.8 mmol) in dichloromethane (5 mL) and 1 drop of DMF (Aldrich, Sure Seal). The reaction was stirred at rt for 1 h. The solvent was removed in vacuo. The title compound was prepared by addition of the acid chloride to 6-amino-s-triazolo(1,5-a)pyridine (0.04 g, 0.3 mmol; prepared by the method of Potts, K. T. and Surapaneni, C. R., J. Heterocyclic Chem., 1970, 7, 1019) and sodium bicarbonate (0.2 g, 2.2 mmol) in acetone (10 mL) and water (1 mL) by general procedure VI. The product was isolated by chromatography on silica gel eluted with chloroform/methanol (95:5, v/v) in 15% yield. MS (ES(+)): m+1/z 443. ¹H NMR (CDCl₃, 300 MHz) δ 9.85 (s, 1H), 9.66 (s, 1H), 8.32 (s, 1H), 7.79 (m, 2H), 7.57 (dd, 1H), 7.4 (m, 3H), 7.15-7.05 (m, 2H), 4.79 (s, 2H).

Example 58:

5 Acid 49 (0.1 g, 0.3 mmol), was converted to the acid chloride by reaction with oxalyl chloride (0.1 ml, 0.8 mmol) in dichloromethane (5 mL) and 1 drop of DMF (Aldrich, Sure Seal). The reaction was stirred at rt for 1 h. The solvent was removed in vacuo. The title compound was prepared by addition of the acid chloride to 6-aminoquinoxaline (0.045 g, 0.3 mmol; prepared by the method of Case, F. H. and Brennan, J. A., JACS, 1959, 81, 6297) and sodium bicarbonate (0.2 g, 2.2 mmol) in acetone (10 mL) and water (1 mL) by
 10 general procedure VI. The product was isolated by chromatography on silica gel eluted with chloroform/methanol (95:5, v/v) in 15% yield. MS (ES(+)): m+1/z 454. ¹H NMR (CDCl₃, 300 MHz) δ 9.78 (s, 1H), 8.82 (s, 1H), 8.76 (s, 1H), 8.64 (s, 1H), 8.18 (dd, 1H), 8.09 (d, 1H), 7.56 (dd, 1H), 7.6 (m, 3H), 7.15-7.05 (m, 2H), 4.79 (s, 2H).

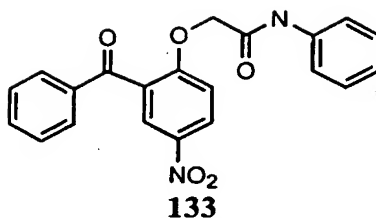
15

Example 59:

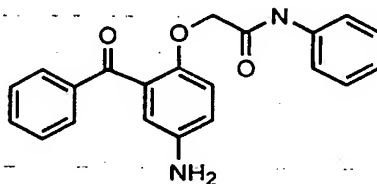
Acid 49 (0.1 g, 0.3 mmol), was converted to the acid chloride by reaction with oxalyl
 20 chloride (0.1 mL, 0.8 mmol) in dichloromethane (5 mL) and 1 drop of DMF (Aldrich, Sure Seal). The reaction was stirred at rt for 1 h. The solvent was removed in vacuo. The title compound was prepared by addition of the acid chloride to 6-amino-1H-imidazo[4,5-b]pyridine (0.04 g, 0.3 mmol; which can be prepared by the method of Brooks, W. and Day, A. R., J. Heterocyclic Chem., 1969, 6(5), 759) and sodium bicarbonate (0.2 g, 2.2
 25 mmol) in acetone (10 mL) and water (1 mL) by general procedure VI. The product was isolated by chromatography on silica gel eluted with chloroform/methanol (9:1, v/v) in 10% yield. MS (ES(+)): m+1/z 443. ¹H NMR (CDCl₃, 300 MHz) δ 9.66 (s, 1H), 8.83 (s, 1H), 8.66 (s, 1H), 8.28 (s, 1H), 7.58 (dd, 1H), 7.4 (m, 3H), 7.15-7.05 (m, 2H), 4.79 (s, 2H).

30

134

Example 60:

5 2-Hydroxy-5-nitrobenzophenone (1.09 g, 4.50 mmol, which can be prepared by the method of Hayashi, I. *et.al.*, Bull.Chem. Soc. Jpn., 1983, 56(8), 2432-7), 2-bromo-N-phenyl acetamide (1.01 g, 4.74 mmol, which can be prepared by the method of Vloon, W. *et.al.*, J.Med.Chem., 1987, 30, 20-24), and potassium carbonate (656 mg, 4.74 mmol) were added to DMF (20 mL). The reaction was stirred for 16 h at rt. The reaction was poured
10 onto ice water and a precipitate formed. The precipitate was filtered and rinsed with water. The product was purified by chromatography on silica gel using a Biotage flash chromatography system, eluting with hexane/ethyl acetate (3:1) to obtain 1 g (2.66 mmol, 59% yield). MS (ES(+)): m+1/z 377, MS (ES(-)): m-1/z 375. ¹H NMR (CDCl₃, 300 MHz) δ 8.96 (s, 1H), 8.46 (dd, 1H), 8.36 (d, 1H), 7.90 (d, 2H), 7.66 (m, 3H), 7.55 (m, 2H),
15 7.34 (t, 2H), 7.19 (d, 1H), 7.13 (t, 1H), 4.79 (s, 2H).

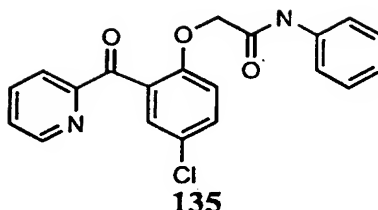
Example 61:

20

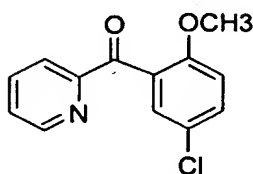
134

Compound 133 (50 mg, 133 mmol) and Raney-Nickel catalyst (Aldrich, 45 mg, 90% by weight) were added to ethanol (30 mL) and placed on a Parr hydrogenator at 50 psig hydrogen pressure. Additional catalyst (100 mg) was added at 1 h intervals. After 3 h, the catalyst was filtered and the solvents removed in vacuo. The product was purified by
25 chromatography on silica gel eluted with chloroform/methanol (98:2) to obtain 38.6 mg (112 mmol, 84% yield). MS (ES(+)): m+1/z 347. ¹H NMR (CDCl₃, 300 MHz) δ 9.06 (s, 1H), 7.90 (d, 2H), 7.60 (m, 3H), 7.48 (m, 2H), 7.30 (t, 2H), 7.09 (t, 1H), 6.90 (d, 1H), 6.84 (dd, 1H), 6.74 (d, 1H), 4.59 (s, 2H), 3.62 (br s, 2H).

135

Example 62:

135

Step A:

136

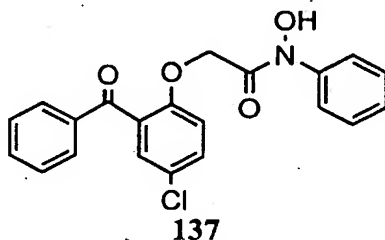
2-Bromo-4-chloroanisole (24.4 g, 0.11 mol) was added dropwise to a stirred suspension of magnesium (2.7 g, 0.11 mol) in diethyl ether (150 mL) containing a crystal of iodine. The mixture was heated to reflux for 2 h. A solution of 2-cyanopyridine (11.4 g, 0.11 mol) in diethyl ether (100 mL) was added dropwise and the resulting suspension (yellowish-tan precipitate formed) was refluxed for 2h, cooled to rt and poured into cold 2N HCl (300 mL). The diethyl ether layer was separated and discarded. The aqueous layer was made basic by addition of 50% aq NaOH and extracted with ether (4 x 300 mL). The combined ether extracts were washed with water, dried over sodium sulfate, and evaporated to give a brown solid. The product was purified by chromatography on silica gel eluted with ethyl acetate/hexane (1:3) to give 10.9 g, in 40% yield. MS (ES⁺) m/z: 248.0 (M+1, 85%), 270 (M+23, 45%); ¹H NMR (CDCl₃, 300 MHz) δ 8.64 (d, 1H), 8.02 (d, 1H), 7.85 (t, 1H), 7.41-7.47 (m, 3H), 6.91 (d, 1H), 3.64 (s, 3H).

Step B:

1-(5-Chloro-2-methoxyphenyl)-1-(2-pyridinyl) methanone (125 mg, 0.505 mmol) was dissolved in dichloromethane (5 mL) and chilled to -78°C in a dry ice/acetone bath. A nitrogen atmosphere was provided. Boron tribromide (1M in CH₂Cl₂, 2 mL, 2 mmol) was added dropwise and the flask warmed to rt overnight. Water (5 mL) was added dropwise, and the contents of the flask were washed once with water, once with brine, dried over sodium sulfate, and solvents removed in vacuo. The crude sample was dissolved in DMF (5 mL). 2-Bromo-N-phenyl acetamide (113 mg, 0.532 mmol, which can be prepared by

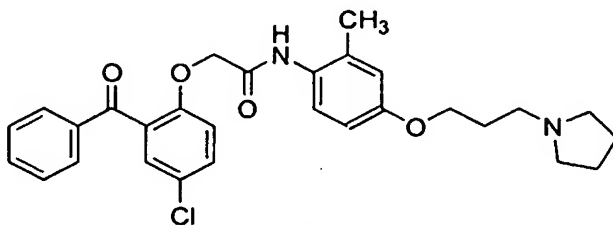
the method of Vloon, W. *et al.*, J. Med. Chem., 1987, 30, 20-24) and potassium carbonate (73.5 mg, 0.532 mmol) were added. After 64 h the contents of the flask were poured onto ice water (50 mL) and the precipitate was filtered. The product was purified by chromatography on silica gel using a Biotage flash chromatography system, eluting with hexane/ethyl acetate (3:1) to obtain 15.5 mg (42.3 μ mol, 8.4% yield over two steps). MS (ES(+)): $m+1/z$ 367. ^1H NMR (CDCl_3 , 300 MHz) δ 9.38 (s, 1H), 8.60 (d, 1H), 8.20 (d, 1H), 7.93 (td, 1H), 7.60 (m, 3H), 7.47 (m, 2H), 7.33 (t, 2H), 7.12 (t, 1H), 6.94 (d, 1H), 4.63 (s, 2H).

Example 63:



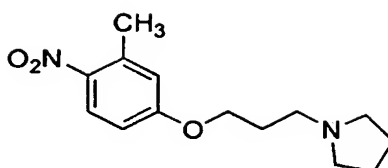
2-(2-Benzoyl-4-chlorophenoxy)acetyl chloride (0.1 g, 0.32 mmol) was dissolved in dry acetonitrile (2 mL). 2-Phenylhydroxylamine (which was prepared by the method outlined in Org. Syn. Col. Vol. I, p.445, 0.35g) was dissolved in ether and dried with MgSO_4 . The mixture was filtered and the ether removed in vacuo. The residue was dissolved in acetonitrile (2 mL) and added to the acid chloride solution. The reaction was stirred at rt for 3 h. A precipitate formed and was filtered. The reaction solvent was removed in vacuo. The product was purified by chromatography on silica gel eluted with hexane/ethyl acetate (3:1, v/v). The product containing fractions were combined and the solvents removed in vacuo to provide a 50% yield. MS (APCI(+)): $m+\text{Na}/z$ 404. ^1H NMR (CDCl_3 , 300 MHz) δ 9.85 (s, 1H), 7.85 -7.0(m, 13H), 4.95 (s, 2H).

Example 64:



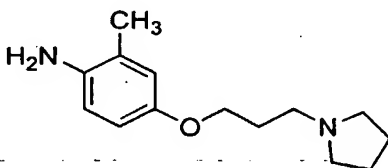
Step A:

137



139

4-(3-bromopropoxy)-2-methyl-1-nitrobenzene (8.0 g, 29.2 mmol, which can be prepared according to the method found in Patent; Wellcome Foundation; GB 982572; 1960; Chem. Abstr.; EN; 63; 2928b; 1965), pyrrolidine (92.5 mL, 29.2 mmol) and K_2CO_3 (5.0 g, 35 mmol) were mixed together in DMF (30 mL) at rt for 16 h. The reaction mixture was filtered and the solvents were removed under reduced pressure to leave an oil and was dissolved in CH_2Cl_2 , washed with aqueous NaOH (1N), water, dried and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 95:5 dichloromethane/methanol as eluant to afford 139 as an orange oil (7.5 g, 97%). 1H NMR ($CDCl_3$, 300 MHz) δ 1.84 (m, 4H), 2.06 (ddd, 2H), 2.57 (m, 6H), 2.58 (s, 3H), 4.14 (t, 2H), 6.84 (m, 3H), 8.10 (d, 1H).

Step B:

140

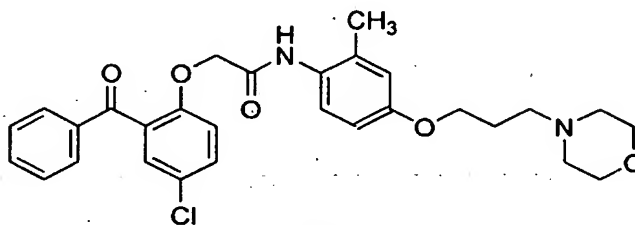
Into a stirred Parr bottle were placed compound 139 (7.5 g, 28.4 mmol), Pd/C (0.75 g, 10%), and EtOH (300 mL). The bottle was pressurized to 5 atm. with hydrogen gas and was allowed to stir at rt for 3 h. The mixture was then filtered through a pad of celite and the solvents were removed under reduced pressure to give 140 as an orange oil (6.0 g, 98%). 1H NMR ($CDCl_3$, 300 MHz) δ 1.84 (m, 4H), 1.98 (ddd, 2H), 2.19 (s, 3H), 2.42 (m, 6H), 3.28 (br s, 1H), 3.98 (t, 2H), 6.84 (m, 3H).

Step C:

Carboxylic acid 105 (1.0 g, 3.9 mmol), amine 140 (1.22 g, 3.9 mmol), HOBt (5.25 g, 3.9 mmol), EDAC (0.9 g, 4.7 mmol), triethylamine (1.3 mL, 3.9 mmol) and DMF (50 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol as eluant to provide 138 as an

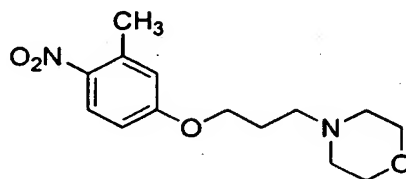
orange oil (0.84 g, 36%). ^1H NMR (CDCl_3 , 300 MHz) δ 2.07 (s, 3H), 2.11 (m, 6H), 2.30 (ddd, 2H), 3.22 (m, 4H), 4.01 (t, 2H), 4.63 (s, 2H), 6.65 (m, 2H), 7.01-7.55 (m, 6H), 7.79 (dd, 2H), 7.98 (s, 1H), 8.13 (s, 1H).

Example 65:



141

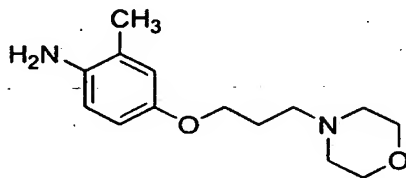
Step A:



142

4-(3-bromopropoxy)-2-methyl-1-nitrobenzene, and morpholine (5.0 g, 18.2 mmol) were used in the same manner as to prepare compound 139. Compound 142 was obtained as an oil (5.1 g, 100%). ^1H NMR (CDCl_3 , 300 MHz) δ 2.02 (ddd, 2H), 2.38-2.56 (m, 6H), 2.64 (s, 3H), 3.73 (m, 4H), 4.11 (t, 2H), 6.81 (m, 2H), 8.09 (d, 1H).

Step B:



143

Compound 142 (5.1 g, 18.2 mmol) was used in the same manner as that to prepare compound 140. Amine 143 was obtained as an oil (4.3 g, 95%). ^1H -NMR (CDCl_3 , 300 MHz) δ 1.94 (ddd, 2H), 2.19 (s, 3H), 2.49-2.54 (m, 6H), 3.39 (br s, 1H), 3.75 (m, 4H), 3.96 (t, 2H), 6.64-6.70 (m, 3H).

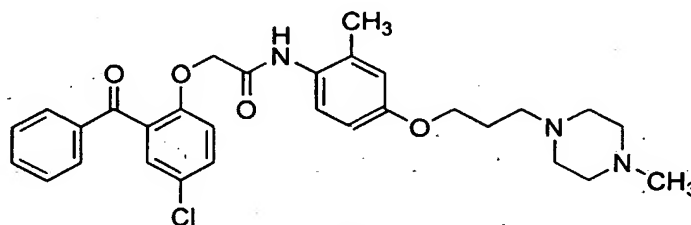
Step C:

Carboxylic acid 105, amine 143, HOBt, EDAC, triethylamine, and DMF were used according to general procedure IV. The product was purified by flash chromatography

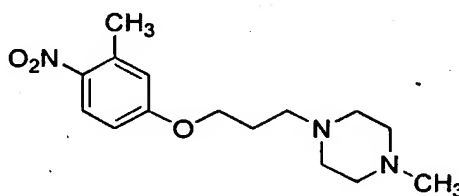
139

using 95:5 dichloromethane/methanol to afford **141** as an oil (1.3 g, 67%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.98 (ddd, 2H), 2.11 (s, 3H), 2.48-2.56 (m, 6H), 3.75 (m, 4H), 4.02 (t, 2H), 4.68 (s, 2H), 6.6-7.37 (m, 9H), 7.86 (d, 2H), 8.11 (s, 1H).

5 **Example 66:**

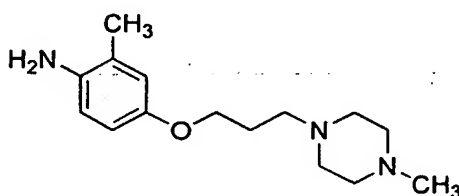
**144**

Step A:

**144**

4-(3-bromo-propoxy)-2-methyl-1-nitro-benzene, and 1-methylpiperazine (5.0 g, 18.2 mmol) were used in the same manner as to prepare compound **139**. Compound **144** was obtained as an oil (3.4 g, 63%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.98 (ddd, 2H), 2.26 (s, 3H), 2.38-2.60 (m, 10H), 2.65 (s, 3H), 4.11 (t, 2H), 6.80 (m, 2H), 8.10 (d, 1H).

15 **Step B:**

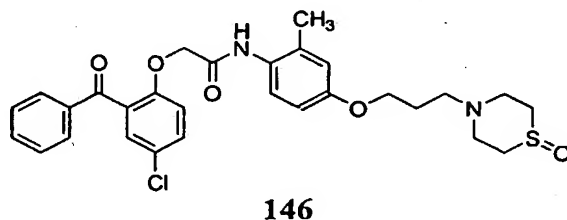
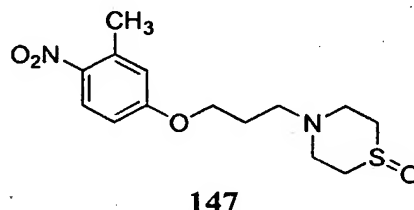
**145**

Compound **144** (3.4 g, 12.5 mmol) was used in the same manner as that to prepare compound **140**. Amine **145** was obtained as an oil (3.1 g, 95%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.88 (ddd, 2H), 2.10 (s, 3H), 2.25 (s, 3H), 2.26-2.65 (m, 10H), 3.35 (br s, 1H), 3.89 (t, 2H), 6.50-6.70 (m, 3H).

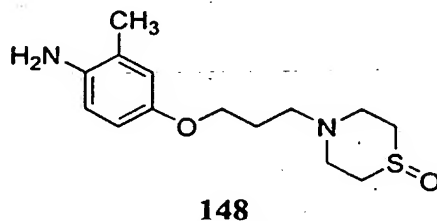
25 **Step C:**

140

Carboxylic acid 105, amine 145, HOBt, EDAC, triethylamine, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford 144 as an oil (0.95 g, 47%). ¹H NMR (CDCl₃, 300 MHz) δ 1.92 (m, 2H), 2.05 (s, 3H), 2.29 (s, 3H), 2.40-2.70 (m, 10H), 3.39 (s, 1H), 3.95 (t, 2H), 4.62 (s, 2H), 6.70 (s, 2H), 6.90 (d, 1H), 6.72-7.60 (m, 5H), 7.81 (d, 2H), 8.06 (s, 1H).

Example 67:**Step A:**

4-(3-bromo-propoxy)-2-methyl-1-nitro-benzene, and thiomorpholine-1-oxide (5.0 g, 18.2 mmol, which can be prepared according to Nachtergaele, Willy A.; Anteunis, Marc J. O.; Bull.Soc.Chim.Belg.; EN; 89; 7; 1980; 525-536) were used in the same manner as to prepare compound 139. Compound 147 was obtained as an oil (2.1 g, 37%). ¹H NMR (CDCl₃, 300 MHz) δ 2.05 (ddd, 2H), 2.65 (s, 3H), 2.63 (t, 2H), 2.65-3.20 (m, 8H), 4.12 (t, 2H), 6.82 (m, 2H), 8.10 (s, 1H).

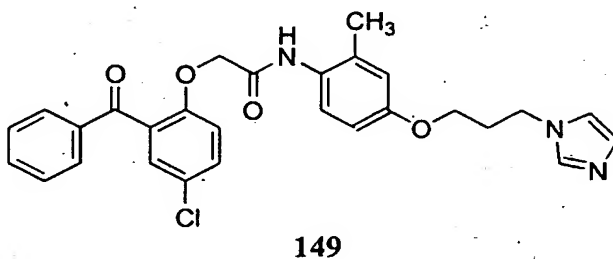
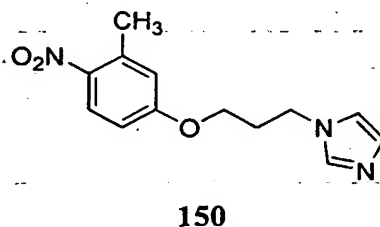
Step B:

Compound 147 (2.1 g, 6.7 mmol) was used in the same manner as that to prepare compound 140. Amine 148 was obtained as an oil (2.1 g, 98%). ¹H NMR (CDCl₃, 300

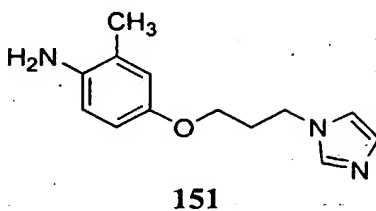
MHz) δ 1.84 (ddd, 2H), 2.15 (s, 3H), 2.58 (t, 2H), 2.65-3.25 (m, 10H), 3.84 (t, 2H), 6.28 (m, 3H).

Step C:

Carboxylic acid **105**, amine **148**, HOBt, EDAC, triethylamine, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **146** as an oil (0.7 g, 32%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.95 (ddd, 2H), 2.71 (s, 3H), 2.63 (t, 2H), 2.65-3.20 (m, 8H), 4.00 (t, 2H), 4.67 (s, 2H), 6.72 (s, 2H), 7.03 (d, 2H), 7.38-7.85 (m, 6H), 7.85 (m, 2H), 8.15 (s, 1H).

Example 68:**Step A:**

4-(3-bromo-propoxy)-2-methyl-1-nitro-benzene, and imidazole (5.0 g, 18.2 mmol) were used in the same manner as to prepare compound **139**. Compound **150** was obtained as an oil (3.1 g, 61%). ^1H NMR (CDCl_3 , 300 MHz) δ 2.35 (ddd, 2H), 2.66 (s, 3H), 3.64 (d, 2H), 4.00 (d, 2H), 6.8 (s, 2H), 6.95 (d, 2H), 7.11 (d, 2H), 7.53 (s, 1H), 8.10 (d, 1H).

Step B:

142

Compound 150 (3.1 g) was used in the same manner as that to prepare compound 140.

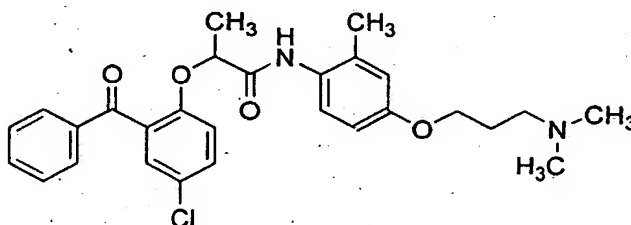
Amine 148 was obtained as an oil (0.71 g, 26%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.27 (ddd, 2H), 2.18 (s, 3H), 3.88 (t, 2H), 4.06 (br s, 1H), 4.25 (t, 2H), 6.60 (m, 3H), 6.98 (d, 2H), 7.13 (d, 2H), 7.13 (d, 2H), 7.82 (s, 1H).

Step C:

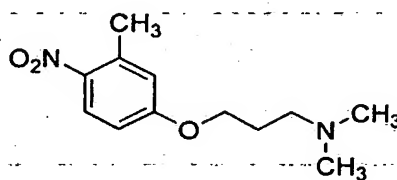
Carboxylic acid 105, amine 151, HOBt, EDAC, triethylamine, and DMF were used according to general procedure IV. The product was purified by flash chromatography

using 95:5 dichloromethane/methanol to afford 149 as an oil (1.1 g, 51%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.27 (ddd, 2 H), 2.18 (s, 3H), 3.80 (t, 2H), 4.18 (t, 2H), 4.63 (s, 2H), 6.60-7.62 (m, 8H), 7.82 (d, 2H), 8.18 (s, 1H).

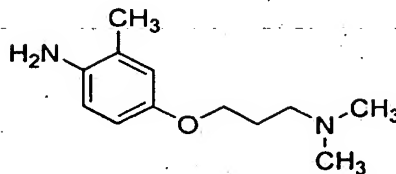
Example 69:



Step A:

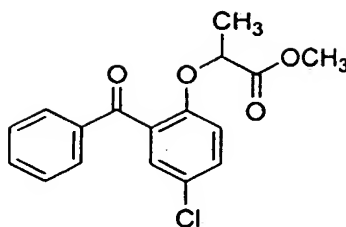


Step B:



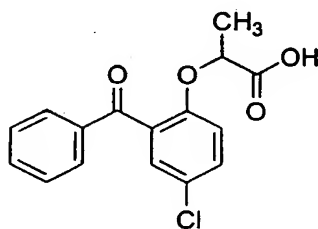
Step C:

143



155

A mixture of 5-chloro-2-hydroxybenzophenone (25 g, 107.4 mmol), methyl 2-bromopropionate, K_2CO_3 (23.0 g, 161 mmol) and acetone (250 mL) were used according to general procedure II to afford **155** as a yellow oil (32.0 g, 94%). 1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (d, 3H), 3.64 (s, 3H), 4.62 (q, 1H), 6.78 (d, 1H), 7.22-7.61 (m, 5H).

Step D:

156

Ester **155** (11 g, 34.5 mmol), water (5 mL) and ethanol (150 mL) were used according to general procedure III, except that sodium hydroxide (5 mL of a 5N solution, 25 mmol) was used in place of lithium hydroxide. Acid **156** was obtained as a brown oil (4.5 g, 43%). 1H NMR ($CDCl_3$, 300 MHz) δ 1.65 (d, 3H), 4.96 (q, 1H), 7.10-7.98 (m, 8H).

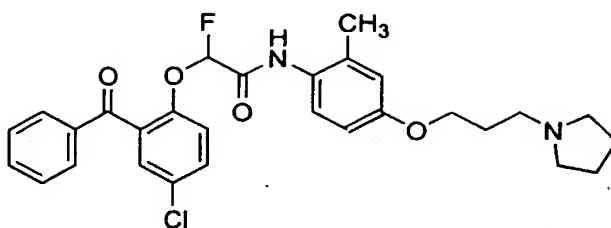
Step E:

Carboxylic acid **156**, amine **154** (0.68 g, 3.3 mmol), EDAC, HOBt and DMF were used according to general procedure IV to afford compound **152** as an orange oil (1.1 g, 61%).

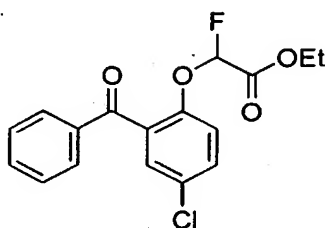
1H NMR ($CDCl_3$, 300 MHz) δ 1.6 (d, 3H), 1.95 (ddd, 2H), 2.05 (s, 3H), 2.26 (s, 6H), 2.45 (t, 2H), 3.88 (t, 2H), 4.92 (q, 1H), 6.64 (m, 9H), 7.84 (d, 2H), 8.22 (s, 1H).

Example 70:

144

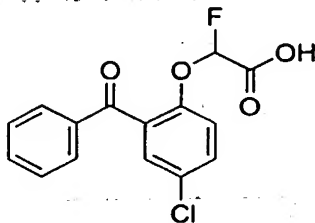


157

Step A:

158

A mixture of 5-chloro-2-hydroxybenzophenone (6.3 g, 27 mmol), ethyl bromofluoroacetate, K_2CO_3 (4.5 g, 32 mmol) and DMF (50 mL) were combined and the reaction mixture was allowed to stir at 80 °C for 24 h. The mixture was then filtered, and poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **158** as an oil (7.0 g, 77%). 1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H), 4.17 (q, 2H), 5.66 (d, 1H), 5.87 (d, 1H), 7.19-8.82 (m, 8H).

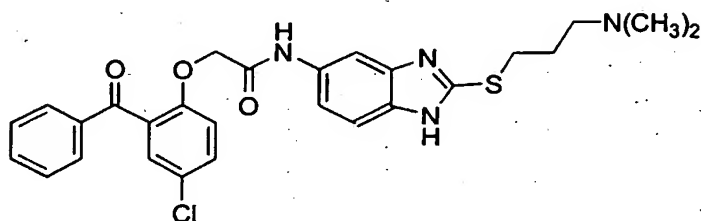
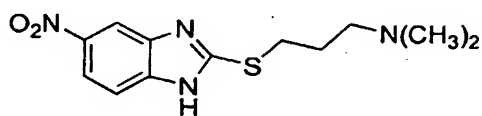
Step B:

159

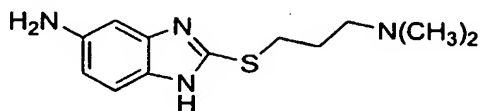
Ester **158**, water, and ethanol (150 mL) were used according to general procedure III, except that sodium hydroxide (5 mL of a 5N aqueous solution) was used in place of lithium hydroxide. The solvents were removed under reduced pressure to afford **159** as white crystals (5.4 g, 84%). 1H NMR ($CDCl_3$, 300 MHz) δ 5.85 (d, 1H), 6.05 (d, 1H), 7.89 (m, 8H).

Step C:

Carboxylic acid **159**, amine **140**, EDAC, HOBt and DMF were used according to general
5 procedure IV to afford **157** as a yellow foam (0.28 g, 17%). ¹H NMR (CDCl₃, 300 MHz) δ
1.92 (m, 4H), 2.08 (ddd, 2H), 2.22 (s, 3H), 2.62-2.85 (m, 6H), 4.03 (t, 2H), 5.96 (d, 1H),
6.16 (d, 1H), 6.73 (br s, 2H), 7.30-7.85 (m, 7H), 7.85 (m, 7H), 8.2 (s, 1H).

Example 71:**160****Step A:****161**

15 Into a round-bottom flask were placed 2-mercapto-5-nitrobenzimidazole (2.0 g, 10.2
mmol), K₂CO₃ (2.8 g, 20.4 mmol) and 3-(N,N-dimethylamino)-1-chloropropane
hydrochloride (1.6 g, 10.2 mmol) and DMF (50 mL). The resulting mixture was allowed
to stir at rt for 24 h, after which time the DMF was removed under reduced pressure to
afford a brown oil. The product was purified by flash chromatography using 9:1
20 dichloromethane/methanol as eluant to afford **161** (1.5 g, 54%). ¹H NMR (CDCl₃, 300
MHz) δ 2.12 (ddd, 2H), 2.24 (s, 6H), 3.68 (t, 2H), 3.28 (t, 2H), 5.28 (s, 1H), 7.24 (dd, 1H),
8.18 (dd, 1H), 8.28 (s, 1H).

Step B:

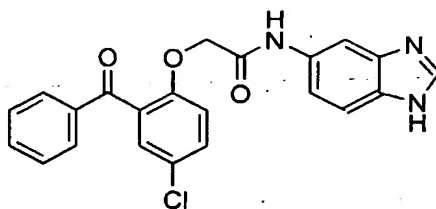
146

162

Into a stirred Parr bottle were placed compound 161 (1.50 g, 5.36 mmol), Pd/C (0.15 g, 10% w/w), and ethanol (300 mL). The bottle was pressurized to 5 atm. with hydrogen gas and the mixture was allowed to stir at rt for 3 h. The mixture was then filtered through a pad of celite and the solvents were removed under reduced pressure to afford 162 as an orange oil (0.80 g, 58%). ¹H NMR (CDCl₃, 300 MHz) δ 1.91 (ddd, 2H), 2.27 (s, 6H), 3.18 (t, 2H), 3.47 (br s, 2H), 3.68 (br s, 2H), 6.54 (dd, 1H), 6.71 (s, 1H), 7.26 (dd, 1H), 8.27 (s, 1H).

Step C:

Carboxylic acid 105, amine 162, EDAC, HOBt, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol as eluant to afford 160 as white crystals (0.24 g, 14%). ¹H NMR (CDCl₃, 300 MHz) δ 2.05 (ddd, 2H), 2.48 (s, 6H), 2.96 (t, 2H), 3.20 (br s, 2H), 4.62 (s, 2H), 5.22 (s, 1H), 6.86-8.20 (m, 11H), 9.00 (s, 1H).

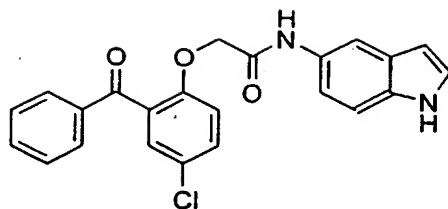
Example 72:

163

Carboxylic acid 105, 5-aminobenzimidazole, HOBt, EDAC and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford 163 as white crystals (0.28 g, 35%). ¹H NMR (CDCl₃, 300 MHz) δ 4.66 (s, 2H), 6.97-8.16 (m, 11H), 9.11 (s, 1H), 10.1 (br s, 1H).

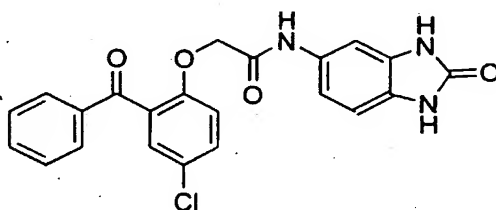
Example 73:

147



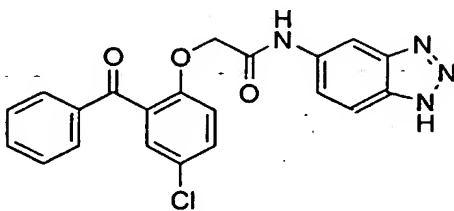
164

Carboxylic acid **105**, 5-aminoindole, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **164** as white crystals (0.25 g, 32%). ¹H NMR (CDCl₃, 300 MHz) δ 4.71 (s, 2H), 6.58 (s, 1H), 7.06-8.72 (m, 14H).

Example 74:

165

Carboxylic acid **105**, 5-aminobenzimidazolone, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **165** as white crystals (0.44 g, 27%). ¹H NMR (CDCl₃, 300 MHz) δ 4.71 (s, 2H), 6.83-7.86 (m, 11H), 9.62 (s, 1H), 10.55 (s, 1H), 10.59 (s, 1H).

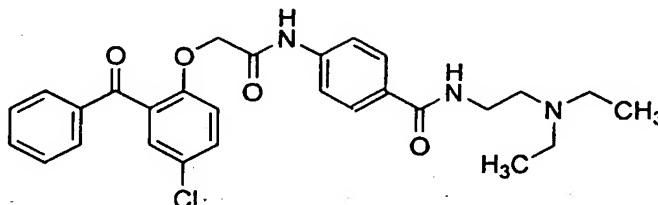
Example 75:

166

Carboxylic acid **105**, 5-aminobenzotriazole, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5

dichloromethane/methanol to afford **166** as white crystals (0.75 g, 91%). ^1H NMR (CDCl_3 , 300 MHz) δ 4.79 (s, 2H), 7.06-8.61 (m, 11H), 9.81 (s, 1H), 12.60 (br s, 1H).

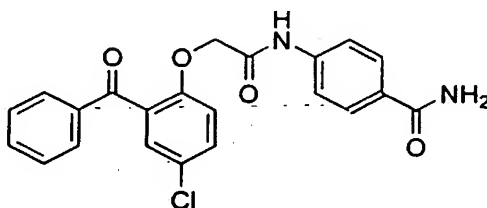
Example 76:



167

Carboxylic acid **105**, N1-[2-(diethylamino)ethyl]-4-aminobenzamide, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **167** as white crystals (0.12 g, 12%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.21 (t, 6H), 2.83 (q, 4H), 2.90 (dd, 2H), 3.66 (dd, 2H), 4.73 (s, 2H), 7.04-7.95 (m, 13H), 9.43 (s, 1H).

Example 77

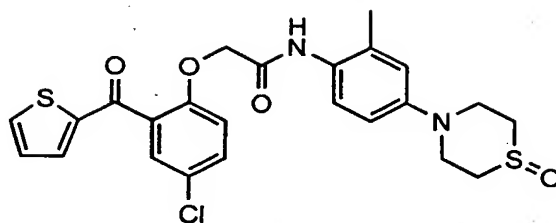


168

Carboxylic acid **105**, 4-aminobenzamide, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **168** as white crystals (0.13 g, 13%). ^1H NMR (CDCl_3 , 300 MHz) δ 4.75 (s, 2H), 5.34 (s, 2H), 7.06-7.97 (m, 12H), 9.53 (s, 1H).

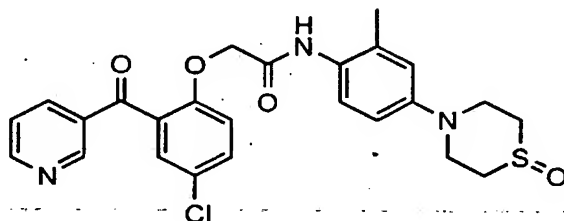
Example 78:

149



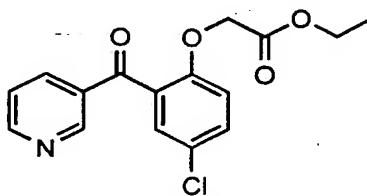
169

Carboxylic acid 112 (0.15 g, 0.51 mmol), amine 399 (0.11 g, 0.51 mmol), HOBt (0.7 g, 0.51 mmol), EDAC (0.98 g, 0.51 mmol), Et₃N (0.14 mL, 0.10 g, 1.0 mmol) and anhydrous DMF (7 mL) were used according to general procedure IV. Treatment of the resulting yellow oil with diethyl ether provided 169 (0.052 g, 20 %) as a yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ 8.99 (s, 1H), 8.08 (d, J= 4.8 Hz, 1H), 7.63 (d, J= 3.2 Hz, 1H), 7.58 (d, J= 9.2 Hz, 1H), 7.50 (s, 1H), 7.20 (m, 3H), 6.84 (s, 1H), 6.78 (d, J= 8 Hz, 1H), 4.75 (s, 2H), 3.70 (m, 2H), 3.54 (m, 2H), 2.87 (m, 2H), 2.64 (m, 2H), 2.02 (s, 3H).

Example 79:

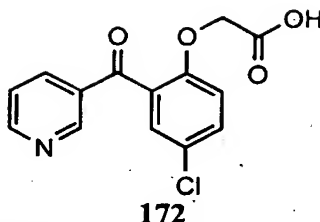
170

15

Step A:

171

Phenol 21 (1.5 g, 6.4 mmol), K₂CO₃ (4.4 g, 32.2 mmol), ethyl bromoacetate (0.79 mL, 1.18 g, 7.1 mmol) and acetone (150 mL) were used according to general procedure II to provide 171 as an oil (4.0 g, >100%). The product was used in the next step without any further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.97 (d, J= 1.6 Hz, 1H), 8.75 (d, J= 4 Hz, 1H), 8.18 (d, J= 7.6 Hz, 1H), 7.43 (m, 3H), 6.78 (d, J= 8.8 Hz, 1H), 4.50 (s, 2H), 4.17 (m, 2H), 1.20 (m, 3H).

Step B:

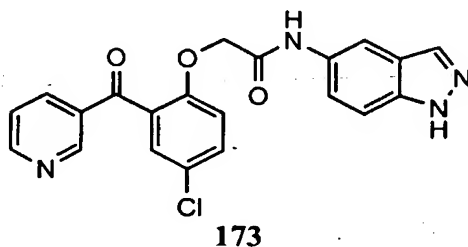
5 Ester 171 (4.0 g, 12.5 mmol), THF (25 mL), water (12 mL), EtOH (12 mL) and LiOH (1.32 g, 31.5 mmol) were used according to general procedure III. Treatment of the resulting yellow gel with ether provided 172 (1.09 g, 29%) as a pale yellow solid. The product was used in the next reaction without any further purification. ¹H NMR (400

10 MHz, DMSO-d₆) δ 8.85 (d, J= 2 Hz, 1H), 8.75 (d, J= 4.8 Hz, 1H), 8.10 (d, J= 8 Hz, 1H), 7.56 (m, 2H), 7.47 (d, J= 2.8 Hz, 1H), 7.10 (d, J= 8.8 Hz, 1H), 4.82 (s, 2H).

Step C:

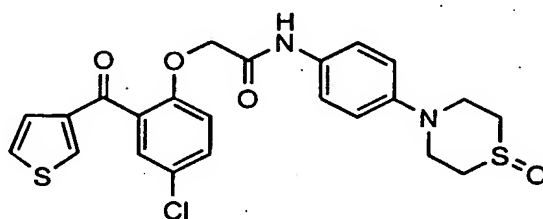
15 Carboxylic acid 172 (0.10 g, 0.34 mmol), amine 399 (0.076 g, 0.34 mmol), HOBt (0.046 g, 0.34 mmol), EDAC (0.19 g, 0.34 mmol), Et₃N (0.1 mL, 0.68 mmol) and anhydrous DMF (5 mL) were used according to general procedure IV. Treatment of resulting oil with diethyl ether provided 170 (0.036 g, 21 %) as a pale yellow solid: ¹H NMR (400

20 MHz, DMSO-d₆) δ 8.99 (s, 1H), 8.88 (s, 1H), 8.75 (s, 1H), 8.10 (d, J= 7.6 Hz, 1H), 7.63 (d, J= 8.8 Hz, 1H), 7.49 (m, 2H), 7.20 (d, J= 8.8 Hz, 1H), 7.05 (d, J= 8.8 Hz, 1H), 6.81 (s, 1H), 6.75 (d, J= 8.8 Hz, 1H), 4.67 (s, 2H), 3.69 (m, 2H), 3.51 (m, 2H), 2.86 (m, 2H), 2.63 (m, 2H), 1.96 (s, 3H).

Example 80:

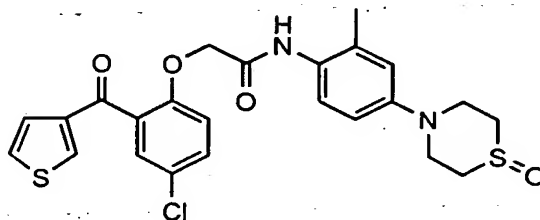
25 Carboxylic acid 172 (0.10 g, 0.34 mmol), 5-aminoindazole (0.045 g, 0.34 mmol), HOBt (0.046 g, 0.34 mmol), EDAC (0.19 g, 0.34 mmol), Et₃N (0.1 mL, 0.68 mmol) and anhydrous DMF (5 mL) were used according to general procedure IV. Treatment of

resulting oil with diethyl ether provided **173** (0.067 g, 49%) as a brown solid: ^1H NMR (400 MHz, DMSO- d_6) δ 12.97 (s, 1H), 9.82 (s, 1H), 8.91 (d, J = 2 Hz, 1H), 8.71 (m, 1H), 8.14 (d, J = 8 Hz, 1H), 7.99 (s, 2H), 7.61 (dd, J = 2.4, 8.8 Hz, 1H), 7.50 (m, 2H), 7.44 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 9 Hz, 1H), 7.19 (d, J = 9 Hz, 1H), 4.70 (s, 2H). MS (ES): 407 (M^+).

Example 81:**174**

Carboxylic acid **119** (0.15 g, 0.51 mmol), amine **399** (0.11 g, 0.51 mmol), HOBt (0.07 g, 0.51 mmol), EDAC (0.1 g, 0.51 mmol), Et₃N (0.14 mL, 1.0 mmol) and anhydrous DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 2% MeOH:CH₂Cl₂ as eluant to provide a yellow oil.

Treatment of the oil with diethyl ether provided **174** (0.065 g, 26%) as a pale yellow solid: ^1H NMR (400 MHz, DMSO- d_6) δ 9.61 (s, 1H), 8.26 (s, 1H), 7.62 (m, 1H), 7.58 (m, 2H), 7.45 (m, 3H), 7.16 (d, J = 9 Hz, 1H), 6.93 (m, 2H), 4.70 (s, 2H), 3.66 (m, 2H), 3.50 (m, 2H), 2.87 (m, 2H), 2.66 (m, 2H). MS (ES): 489 (M^+).

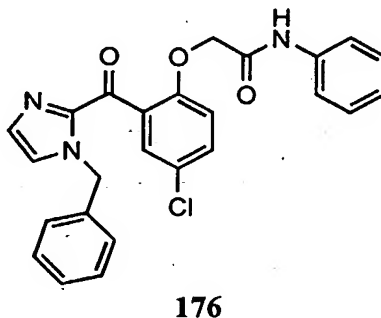
Example 82:**175**

Carboxylic acid **119** (0.15 g, 0.51 mmol), amine **399** (0.11 g, 0.51 mmol), HOBt (0.07 g, 0.51 mmol), EDAC (0.1 g, 0.51 mmol), Et₃N (0.14 mL, 1.0 mmol) and anhydrous DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 2% MeOH:CH₂Cl₂ as eluant to provide a yellow oil.

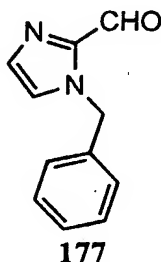
Treatment of the oil with diethyl ether provided **175** (0.046 g, 18%) as a pale yellow solid:

¹H NMR (400 MHz, DMSO-d₆) δ 8.94 (s, 1H), 8.24 (s, 1H), 7.58 (m, 2H), 7.49 (s, 1H), 7.42 (s, 1H), 7.18 (m, 2H), 6.78 (m, 2H), 4.73 (s, 2H), 3.69 (m, 2H), 3.54 (m, 2H), 2.87 (m, 2H), 2.65 (m, 2H), 2.01 (s, 3H). MS (ES): 503 (M⁺).

5 **Example 83:**



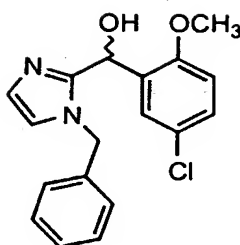
Step A:



10 In a round bottom flask equipped with a stir bar, an addition funnel and nitrogen on demand, were placed 1-benzylimidazole (2.0 g, 12.6 mmol) and anhydrous THF (50 mL) and cooled to -78 °C by means of a dry ice/ acetone bath. n-Butyllitium (8.8 mL of a 1.6 M soln. in hexanes, 13.7 mmol) was added dropwise and the reaction was allowed to stir
15 for 15-20 min at -78 °C. Anhydrous N,N-dimethylformamide (1.3 mL, 0.0013 mmol) was added dropwise and reaction was allowed to stir for an additional 45 min at -78 °C. When judged to be complete, the reaction was quenched by dropwise addition of water and extracted with EtOAc. The organics were dried over Na₂SO₄, filtered and concentrated
20 under reduced pressure to provide 177 (2.1 g, 88 %) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 9.68 (s, 1H), 7.73 (s, 1H), 7.30 (m, 4H), 7.16 (d, J= 7 Hz, 2H), 5.57 (s, 2H).

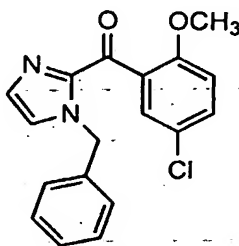
Step B:

153



178

In a round bottom flask equipped with a stir bar, an addition funnel and nitrogen on demand, were placed 2-bromo-4-chloroanisole (1.5 mL, 2.4 g, 11.4 mmol) and diethyl ether (17 mL) and cooled to -78°C by means of a dry ice/ acetone bath. n-Butyllithium (7.8 mL of a 1.6 M soln. in hexanes, 12.5 mmol) was added in a dropwise manner via addition funnel and the reaction was allowed to stir for 30 min at -78°C , after which time the reaction was quenched by dropwise addition of water and extracted with EtOAc. The organics were collected, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to provide 178 (1.5 g, 42 %) as a white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.27 (m, 4H), 7.16 (m, 1H), 7.00 (m, 3H), 6.83 (d, $J=2.4$ Hz, 1H), 6.71 (dd, $J=3, 9$ Hz, 1H), 6.11 (d, $J=2.4$ Hz, 1H), 5.07 (m, 2H), 4.49 (bs, 1H), 3.73 (s, 3H).

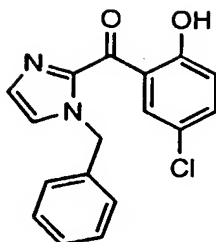
Step C:

179

In a round bottom flask equipped with a stir bar and nitrogen on demand was placed alcohol 178 (1.5 g, 4.6 mmol), CH_2Cl_2 (55 mL) and MnO_2 (4.0 g, 46 mmol). The reaction was allowed to stir at RT for 30 min, after which time, the reaction was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to provide 179 (1.5 g, >99 %) as a clear gel: ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, $J=4$ Hz, 1H), 7.37 (m, 4H), 7.32 (m, 3H), 7.11 (s, 1H), 6.91 (d, $J=12$ Hz, 1H), 5.71 (s, 2H), 3.75 (s, 3H).

Step D:

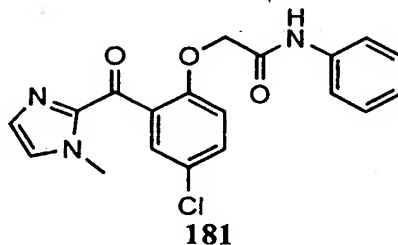
154

**180**

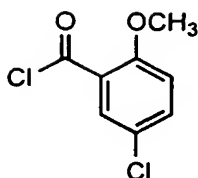
Anisole **179** (1.5 g, 4.6 mmol), CH_2Cl_2 (30 mL) and BBR_3 (12 mL of a 1.0 M soln. in CH_2Cl_2 , 11.5 mmol) were used according to general procedure IX. The resulting brown oil was filtered through a pad of silica gel using CH_2Cl_2 as eluant and the solvents were removed under reduced pressure to provide **180** (0.9 g, 64%) as a yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 8.48 (s, 1H), 7.34 (m, 9H), 6.96 (d, $J = 9$ Hz, 1H), 5.65 (s, 2H).

Step E:

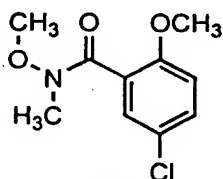
In a round bottom flask equipped with a stir bar, reflux condenser and nitrogen on demand were added the phenol **180** (0.1 g, 0.32 mmol), acetone (7 mL), K_2CO_3 (0.22 g, 1.6 mmol) and 2'-chloroacetanilide (0.058 g, 0.34 mmol). The reaction was allowed to stir at reflux for 18-24 h, after which it was poured into a separatory funnel containing water and ethyl acetate. The organics were collected, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting product was purified by flash chromatography using 3:1 hexanes/ethyl acetate to 1:3 hexanes/ethyl acetate as a solvent gradient to provide **176** (0.077 g, 54 %) as a white solid: ^1H NMR (300 MHz, CDCl_3) δ 10.17 (s, 1H), 7.70 (m, 3H), 7.39 (m, 1H), 6.94 (d, $J = 9$ Hz, 1H), 5.79 (s, 2H), 4.71 (s, 2H). MS(ES): 445(M^+), 446 ($\text{M}+\text{H}$) $^+$.

Example 84:**181****Step A:**

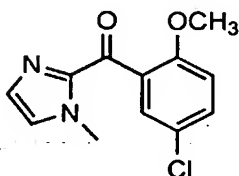
155

**182**

5-Chloro-*o*-anisic acid (7.5 g, 40.2 mmol), CH₂Cl₂ (75 mL), oxalyl chloride (3.7 mL, 5.3 g, 42.2 mmol), and N,N-dimethylformamide (4-5 drops) were used according to general procedure V to afford **182** (8.0 g, 97%) as a yellow oil. The product was used in the next step without further purification or characterization.

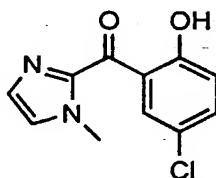
Step B:**183**

Acid chloride **182** (8.0 g, 39 mmol), N,O-dimethylhydroxylamine hydrochloride (7.6 g, 78.0 mmol), CHCl₃ (100 mL), and triethylamine (27 mL, 19.7 g, 195 mmol) were used according to general procedure VII. The resulting colorless oil was treated with diethyl ether to provide **183** (6.0 g, 67 %) as a white solid. The product was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 7.40 (d, J= 8.4 Hz, 1H), 7.27 (d, J= 2.4 Hz, 1H), 3.75 (s, 3H), 3.42 (bs, 3H), 3.19 (bs, 3H). MS (ES): 229(M⁺).

Step C:**184**

In a round bottom flask equipped with a stir bar, an addition funnel and nitrogen on demand, 1-methylimidazole (2.0 g, 24.4 mmol) was dissolved in diethyl ether (50 mL) and cooled to -78 °C by means of a dry ice/ acetone bath. N-Butyllithium (15 mL of a 1.6 M soln. in hexanes, 24.4 mmol) was added dropwise and the reaction was allowed to stir for 30 min at -78 °C. Amide **183** (5.1 g, 22.2 mmol) was added as a solid maintaining

reaction temp at -78°C . When judged to be complete, the reaction was quenched by dropwise addition of water and extracted with EtOAc. The organics were collected, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting product was purified by flash chromatography using 1:1 hexanes/ethyl acetate to provide **184** (3.3 g, 55 %): ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.60 (s, 1H), 7.53 (dd, $J=3, 9$ Hz, 1H), 7.42 (d, $J=3$ Hz, 1H), 7.17 (m, 1H), 7.13 (s, 1H), 4.03 (s, 3H), 3.73 (s, 3H).

Step D:**185**

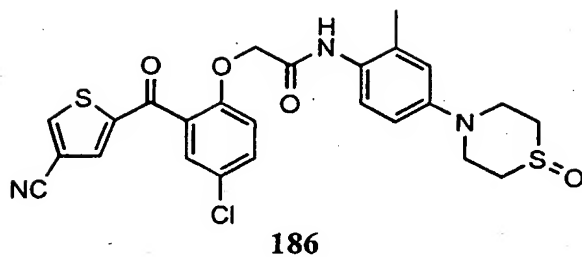
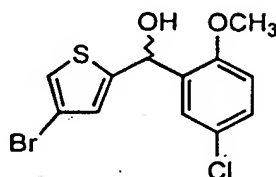
Anisole **184** (3.3 g, 13.2 mmol), CH_2Cl_2 (60 mL), and BBr_3 (53 mL of a 1.0 M soln. in CH_2Cl_2 , 53 mmol) were used according to general procedure IX to provide **185** (2.0 g, 69%) as a yellow solid. The product was used in the next step without further purification. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.90 (s, 1H), 7.83 (d, $J=2$ Hz, 1H), 7.62 (s, 1H), 7.56 (dd, $J=3, 9$ Hz, 1H), 7.04 (d, $J=9$ Hz, 1H), 4.03 (s, 3H).

Step E:

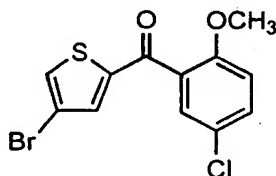
In a round bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand were added the phenol **185** (0.15 g, 0.67 mmol), acetone (5 mL), K_2CO_3 (0.46 g, 3.3 mmol), and the amide **142** (0.12 g, 0.70 mmol). The reaction was allowed to stir at reflux for 18-24 h, after which time the reaction was poured into a separatory funnel containing water and ethyl acetate. The organics were collected, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by flash chromatography using 3:1 hexanes/EtOAc to 1:3 hexanes/EtOAc as a solvent gradient to provide **181** (0.065 g, 25 %) as a white solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.06 (s, 1H), 7.55 (m, 5H), 7.29 (t, $J=8$ Hz, 2H), 7.10 (m, 3H), 4.74 (s, 2H), 4.02 (s, 3H).

Example 85:

157

**Step A:**

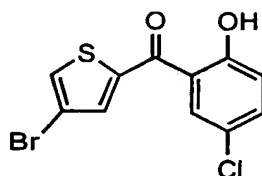
In a round bottom flask equipped with a stir bar, an addition funnel and nitrogen on demand was added 2-bromo-4-chloroanisole (9.8 mL, 15.7 g, 71.3 mmol) and anhydrous THF (120 mL) and the reaction was cooled to -78°C by means of a dry ice/ acetone bath. N-Butyllitium (45 mL of a 1.6 M soln. in hexanes, 72 mmol) was added dropwise and the reaction was allowed to stir for 30 min at -78°C . 4-Bromo-2-thiophenecarboxaldehyde (15 g, 79 mmol) was added and the reaction temperature was maintained at -78°C . When judged to be complete, the reaction was quenched by dropwise addition of water and extracted with ethyl acetate. The organics were collected, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to provide **187** (16.3 g, 62%). The product was used in the next step without further purification or characterization.

Step B:

In a round bottom flask equipped with a stir bar and nitrogen on demand were placed the alcohol **187** (16.3 g, 49 mmol), CH_2Cl_2 (200 mL), and MnO_2 (21.1 g, 240 mmol). The reaction was allowed to stir at RT for 18-24h, after which time the mixture was filtered through a pad of celite and the solvents were removed under reduced pressure to provide **188** (2.3 g, 14 %) as an orange oil. The product was used in the next step without further

purification. ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.55 (m, 1H), 7.45 (m, 2H), 7.19 (d, $J = 9$ Hz, 1H), 3.72 (s, 3H).

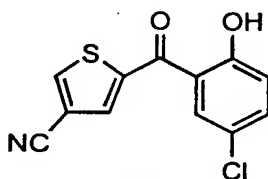
Step C:



189

Anisole 188 (2.3 g, 7.0 mmol), CH_2Cl_2 (100 mL), and BBr_3 (21 mL of a 1.0 M soln. in CH_2Cl_2 , 21 mmol) were used according to general procedure to provide 189 (2.1 g, 94%) as a yellow solid. The product was used without further purification in the next step. ^1H NMR (300 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.24 (s, 1H), 7.57 (d, $J = 1.2$ Hz, 1H), 7.46 (m, 2H), 7.02 (d, $J = 9$ Hz, 1H).

Step D:

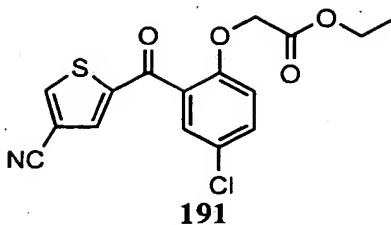


190

In a round bottom flask equipped with a stir bar and nitrogen on-demand was added the phenol 189 (2.1 g, 6.6 mmol), N-methylpyrrolidinone (100 mL), and CuCN (1.2 g, 13.2 mmol) and the reaction was heated to reflux for 2-5h. When judged to be complete, the reaction was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, treated with activated carbon, dried over Na_2SO_4 , filtered through a pad of celite and the solvents were removed under reduced pressure. The resulting brown oil was purified by flash chromatography using 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as eluant to provide 190 (0.5 g, 29 %) as a yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 11.17 (s, 1H), 8.26 (s, 1H), 7.85 (s, 1H), 7.79 (s, 1H), 7.51 (d, $J = 9$ Hz, 1H), 7.05 (d, $J = 9$ Hz, 1H).

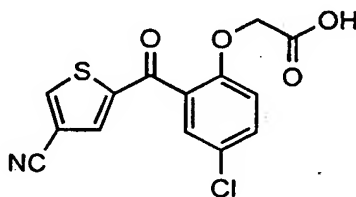
Step E:

159

**191**

Phenol **190** (0.5 g, 1.9 mmol), K_2CO_3 (0.66 g, 4.7 mmol), ethyl bromoacetate (0.2 mL, 0.32 g, 1.9 mmol) and acetone (20 mL) were used according to general procedure II to provide **191** as a clear oil (0.7 g, >100%). The product was used in the next step without further purification. 1H NMR (300 MHz, $DMSO-d_6$) δ 9.00 (s, 1H), 8.09 (s, 1H), 7.62 (dd, $J = 3, 9$ Hz, 1H), 7.54 (d, $J = 3$ Hz, 1H), 7.17 (d, $J = 9$ Hz, 1H), 4.81 (s, 2H), 4.07 (m, 2H), 1.21 (m, 3H).

10

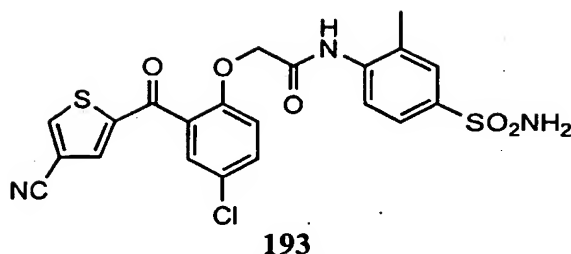
Step F:**192**

Ester **191** (0.7 g, 2 mmol), THF (10 mL), water (5 mL), EtOH (5 mL) and LiOH (0.2 g, 5 mmol) were used according to general procedure III to provide **192** (0.5 g, 80 %) as an orange gel. The product was used in the next step without further purification or characterization.

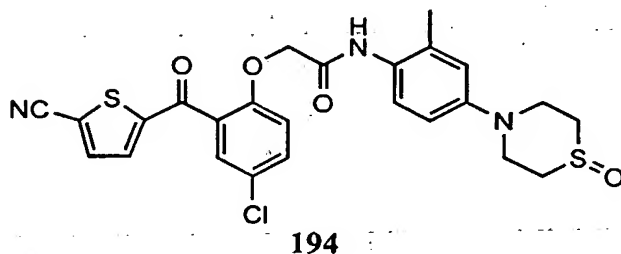
20 **Step G:**

Carboxylic acid **192** (0.16 g, 0.49 mmol), amine 399 (0.13 g, 0.34 mmol), HOBT (0.079 g, 0.34 mmol), EDAC (0.14 g, 0.34 mmol) and anhydrous DMF (7 mL) were used according to general procedure IV. Treatment of resulting product with diethyl ether provided **186** (0.052 g, 21 %) as a pale yellow solid: 1H NMR (400 MHz, $DMSO-d_6$) δ 9.11 (s, 1H), 8.94 (s, 1H), 8.12 (s, 1H), 7.62 (d, $J = 9$ Hz, 1H), 7.53 (d, $J = 2.4$ Hz, 1H), 7.20 (d, $J = 9$ Hz, 1H), 7.14 (d, $J = 9$ Hz, 1H), 6.84 (s, 1H), 6.77 (d, $J = 8$ Hz, 1H), 4.77 (s, 2H), 3.70 (m, 2H), 3.52 (m, 2H), 2.87 (m, 2H), 2.63 (m, 2H), 2.03 (s, 3H). MS(ES): 528 (M^+).

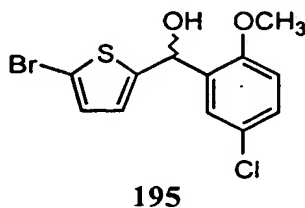
160

Example 86:

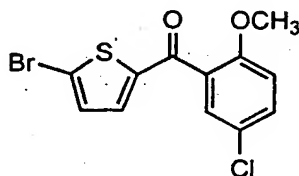
- 5 In a round bottom flask equipped with a stir bar and nitrogen on demand was added the acid **192** (0.36 g, 1.1 mmol), CH_2Cl_2 (20 mL) and oxalyl chloride (0.1 mL, 0.14 g, 1.1 mmol). The mixture was cooled to 0 °C and N,N-dimethylformamide (1-2 drops) was added. The reaction was allowed to warm to rt over a period of 30-60 min, after which
- 10 the mixture was concentrated under reduced pressure to afford the acid chloride. The acid chloride, acetonitrile (20 mL), triethylamine (0.4 mL, 0.29 g, 2.9 mmol) and the sulfonamide (0.26 g, 1.4 mmol) were combined and allowed to stir at RT for 18-24 h. When judged to be complete, the reaction was poured into a separatory funnel containing water and ethyl acetate. The organics were collected, dried over Na_2SO_4 , filtered and the solvents were removed under reduced pressure. The resulting gel was treated with diethyl
- 15 ether to provide **193** (0.11 g, 20%) as a pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.95 (s, 1H), 8.11 (s, 1H), 7.61 (m, 6H), 7.23 (s, 2H), 4.87 (s, 2H), 2.23 (s, 3H).

Example 87:

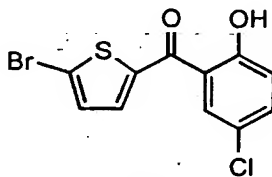
20

Step A:

In a round bottom flask equipped with a stir bar, an addition funnel and nitrogen on demand was added 2-bromo-4-chloroanisole (9.8 mL, 15.7 g, 71.3 mmol) and diethyl ether (250 mL). The reaction was cooled to -78°C by means of a dry ice/acetone bath, and n-butyllithium (45 mL of a 1.6 M soln. in hexanes, 72 mmol) was added dropwise, the reaction was allowed to stir for 30 min at -78°C , after which 5-bromo-2-thiophenecarboxaldehyde (15 g, 79 mmol) was added. When judged to be complete, the reaction was quenched by dropwise addition of water and extracted with ethyl acetate. The organics were collected, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to provide **195** (20 g, 77%). The product was used in the next step without further purification or characterization.

Step B:**196**

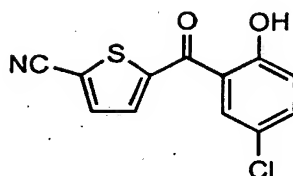
To a round bottom flask equipped with a stir bar and nitrogen on demand was added the alcohol **195** (20 g, 60 mmol), CH_2Cl_2 (300 mL), and MnO_2 (15.6 g, 180 mmol). The reaction was allowed to stir at RT for 90 min, after which time it was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to provide **196** (15.3 g, 77 %) as a pale yellow oil. The product was used in the next step without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.55 (m, 1H), 7.42 (s, 1H), 7.33 (t, $J=3, 9$ Hz, 1H), 7.26 (t, $J=3$ Hz, 1H), 7.17 (m, 1H), 3.72 (s, 3H).

Step C:**197**

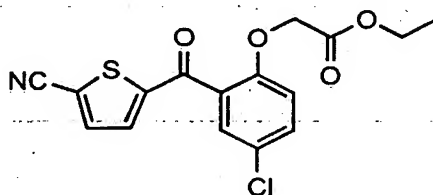
Anisole **196** (8.2 g, 25 mmol), CH_2Cl_2 (175 mL), and BBr_3 (74 mL of a 1.0 M soln. in CH_2Cl_2 , 74 mmol) were used according to general procedure IX to provide **197** (6.8 g, 87%). The product was used in the next step without further purification. ^1H NMR (400

162

MHz, DMSO- d_6) δ 10.35 (s, 1H), 7.39 (dd, J = 2.4, 6 Hz, 1H), 7.35 (m, 4H), 6.94 (dd, J = 3, 9 Hz, 1H).

Step D:**198**

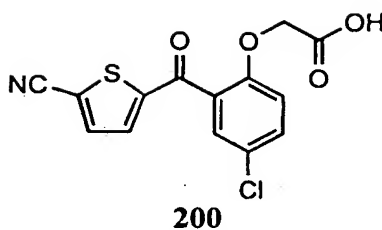
In a round bottom flask equipped with a stir bar and nitrogen on demand was added the phenol **197** (8.5 g, 27 mmol), N-methylpyrrolidinone (350 mL), and copper (I) cyanide (4.8 g, 54 mmol) and the reaction mixture was heated to reflux for 2-5h. When judged to be complete, the reaction was allowed to cool to rt and poured into a beaker containing ethyl acetate and water. The organics were collected, treated with activated carbon, dried over Na_2SO_4 , filtered through a pad of celite and the solvents were removed under reduced pressure. The resulting brown oil was purified by flash chromatography using 5% MeOH/ CH_2Cl_2 as eluant to provide **198** (6.8 g, 21 %) as a yellow solid: ^1H NMR (300 MHz, DMSO- d_6) δ 10.57 (s, 1H), 8.04 (t, J = 2 Hz, 1H), 7.68 (m, 1H), 7.48 (m, 2H), 7.03 (d, J =8.4 Hz, 1H). MS (ES): 262 (M-H).

Step E:**199**

Phenol **198** (1.5 g, 5.7 mmol), K_2CO_3 (3.9 g, 29 mmol), ethyl bromoacetate (0.7 mL, 1.1 g, 6.3 mmol) and acetone (125 mL) were used according to general procedure II to provide **199** as a clear oil (2.0 g, >100%). The product was used in the next step without further purification or characterization.

Step F:

163

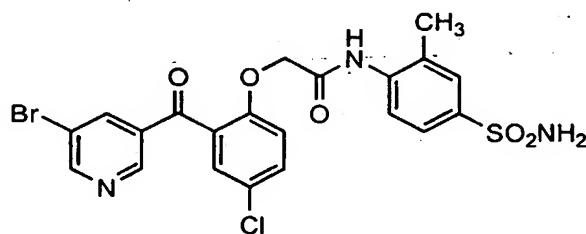


Ester **199** (2.0 g, 5.7 mmol), THF (20 mL), water (10 mL), EtOH (10 mL) and LiOH (1.0 g, 22.8 mmol) were used according to general procedure III to provide **200** (0.42 g, 23 %) as an orange gel. The product was used in the next step without further purification or characterization.

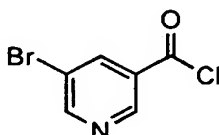
Step G:

Carboxylic acid **200** (0.42 g, 1.3 mmol), amine **399** (0.36 g, 1.6 mmol), HOBt (0.22 g, 1.6 mmol), EDAC (0.38 g, 2.0 mmol) and anhydrous DMF (7 mL) were used according to general procedure IV. The resulting brown oil was purified by flash chromatography using 2 % MeOH/CH₂Cl₂ as eluant. Treatment of the resulting product with diethyl ether provided **194** (0.071 g, 10 %) as a white solid: ¹H NMR (300 MHz, DMSO-d₆) δ 9.08 (s, 1H), 7.83 (d, J = 4.5 Hz, 1H), 7.69 (m, 2H), 7.61 (s, 1H), 7.27 (d, J = 9 Hz, 1H), 7.18 (d, J = 9 Hz, 1H), 6.90 (s, 1H), 6.83 (d, J = 8.4 Hz, 1H), 4.80 (s, 2H), 3.76 (m, 2H), 3.58 (m, 2H), 2.93 (m, 2H), 2.71 (m, 2H), 2.07 (s, 3 H).

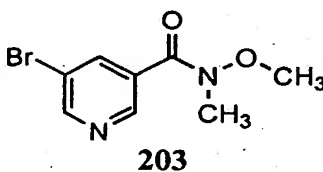
Example 88:



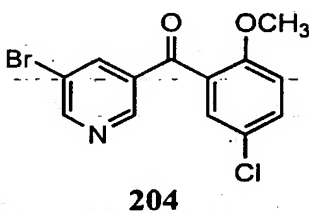
Step A:



5-Bromonicotinic acid (5.0g, 0.025 mol), oxalyl chloride (2.4 mL, 3.5g, 0.027 mol), methylene chloride (125 mL), and N,N-dimethylformamide (2 drops) were used according to general procedure V to provide **202** (6.0g, >100%) as a white solid. The product was used in the next step without further purification. ¹H NMR (300 MHz, DMSO-d₆) δ 9.04 (d, J= 1.5 Hz, 1H), 8.97 (d, J= 2.1 Hz, 1H), 8.44 (t, J= 1.8 Hz, 1H).

Step B:

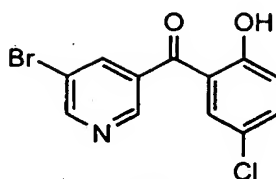
10 Acid chloride **202** (4.0 g, 0.018 mol), N,O-dimethylhydroxylamine hydrochloride (3.5 g, 0.036 mol), Et₃N (7.5 mL, 5.5 g, 0.054 mol), and CHCl₃ (150 mL) were used according to general procedure VII to provide **203** (3.2 g, 74%) as a yellow oil. The product was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 8.79 (d, J= 2 Hz, 1H), 8.72 (d, J= 1.6 Hz, 1H), 8.20 (t, J= 2 Hz, 1H), 3.53 (s, 3H), 3.25 (s, 3H).

Step C:

20 Amide **203** (1.8 g, 7.3 mmol), n-butyllithium (5.0 mL of a 1.6 M soln. in hexanes, 8.0 mmol), 2-bromo-4-chloroanisole (1.0 mL, 1.6 g, 7.3 mmol), and diethyl ether (20 mL) were used according to general procedure VIII. The product was purified by flash chromatography using 7:3 hexanes:ethyl acetate as eluant to afford **204** (1.5 g, 63%) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.93 (d, J= 2.4 Hz, 1H), 8.71 (d, J= 2 Hz, 1H), 8.21 (t, J= 2 Hz, 1H), 7.63 (dd, J=2.8, 9.2 Hz, 1H), 7.48 (d, J=2.8 Hz, 1H), 7.22 (d, J=9.2 Hz, 1H), 3.65 (s, 3H).

Step D:

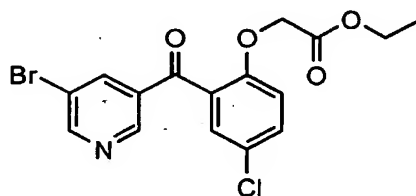
165



205

Anisole **204** (2.0 g, 6.1 mmol), BBr_3 (18.4 mL of a 1.0 M soln. in CH_2Cl_2 , 18.4 mmol), and CH_2Cl_2 (50 mL) were used according to general procedure IX to afford **205** (3.4 g, >100%) as a yellow foam. The product was used in the next step without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.57 (s, 1H), 8.91 (d, $J=2.4$ Hz, 1H), 8.75 (d, $J=1.6$ Hz, 1H), 8.21 (t, $J=2$ Hz, 1H), 7.48 (dd, $J=2.8, 8.8$ Hz, 1H), 7.41 (d, $J=2.8$ Hz, 1H), 6.97 (d, $J=8.8$ Hz, 1H). MS (ES): 314 ($\text{M}+\text{H}$) $^+$, 312 ($\text{M}-\text{H}$) $^-$.

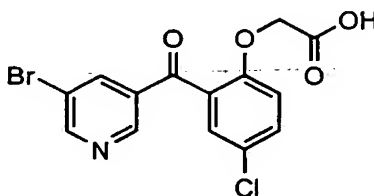
Step E:



206

Phenol **205** (0.55 g, 1.7 mmol), ethyl bromoacetate (0.21 mL, 0.32 g, 1.9 mmol), K_2CO_3 (0.73 g, 5.3 mmol), and acetone (25 mL) were used according to general procedure II to provide **206** (0.58 g, 83%) as a red oil. The product was used in the next step without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.97 (d, $J=2.4$ Hz, 1H), 8.84 (d, $J=1.8$ Hz, 1H), 8.30 (t, $J=1.8$ Hz, 1H), 7.66 (dd, $J=2.7, 9$ Hz, 1H), 7.57 (d, $J=2.7$ Hz, 1H), 7.19 (d, $J=9$ Hz, 1H), 4.82 (s, 2H), 4.18 (m, 2H), 1.2 (m, 3H).

Step F:



207

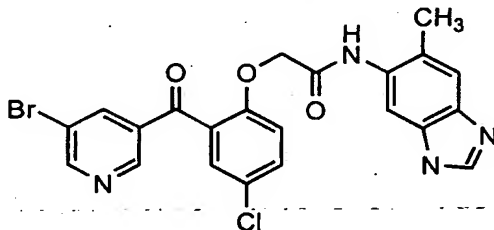
Ester **206** (0.58 g, 1.45 mmol), LiOH (0.15 g, 3.64 mmol) and a solution of THF, EtOH, and water (20 mL) were used according to general procedure III. The resulting orange

residue was treated with diethyl ether to afford **207** (0.2 g, 42%) as a yellow solid. The product was used the next step without further purification or characterization.

Step G:

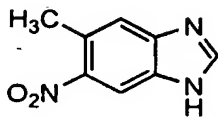
Acid **207** (91 mg, 0.25 mmol), oxalyl chloride (0.023 mL, 33 mg, 0.26 mmol), N,N-dimethylformamide (1 drop), and CH₂Cl₂ (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **466** (42 mg, 0.23 mmol), NaHCO₃ (105 mg, 1.25 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The resulting yellow residue was washed with several portions of diethyl ether to afford **201** (20 mg, 15%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.41 (s, 1H), 8.89 (d, J= 2.4 Hz, 1H), 8.83 (d, J= 1.6 Hz, 1H), 8.29 (t, J=2 Hz, 1H), 7.65 (dd, J=2.8, 8.8 Hz, 1H), 7.62 (s, 1H), 7.58 (m, 2H), 7.53 (d, J=2.8 Hz, 1H), 7.22 (m, 3H), 4.79 (s, 2H), 2.15 (s, 3H). MS (ES): 538 (M-H).

Example 89:



208

Step A:

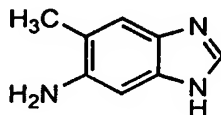


209

To a round-bottom flask equipped with a stir bar was added 5-methylbenzimidazole (4.0 g, 0.030 mol), and concentrated H₂SO₄ (65 mL). The reaction was cooled to 0 °C and potassium nitrate (2.75 g, 0.027 mol) was added portion-wise. After stirring for 1 h, the reaction was poured over ice and solid Na₂CO₃ was added to adjust to pH >8. The aqueous layer was extracted with ethyl acetate, the organics were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to afford a yellow solid. The solid was

recrystallized using 1:1 methanol:water, making sure to filter any undissolved material while mixture was hot, to obtain **209** (1.8 g, 34 %) as a pale yellow solid. ¹H NMR (300 MHz, DMSO-d₆) δ 12.96 (bs, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.65 (s, 1H), 2.64 (s, 3H). MS (ES): 222 (M-H)⁺.

5.

Step B:**210**

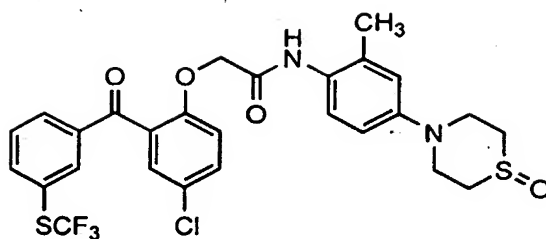
- 10 To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **209** (2.2 g, 0.012 mol), absolute ethanol (75 mL), and palladium on charcoal (0.23 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 50 psig for 16 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide a residue. The residue
- 15 was washed several times with diethyl ether to afford **210** (1.0g, 57%) as a pink solid. At ambient temperature, the product exists as a mixture of tautomers. ¹H NMR (300 MHz, DMSO-d₆, 100 °C) δ 11.60 (bs, 1H), 7.79 (s, 1H), 7.20 (s, 1H), 6.82 (s, 1H), 4.39 (bs, 2H), 2.20 (s, 3H). MS (ES): 148 (M+H)⁺.

20 **Step C:**

- Acid **207** (0.1 g, 0.27 mmol), HOBt (40 mg, 0.27mmol), EDAC (52 mg, 0.27 mmol), , aniline **210** (40 mg, 0.27 mmol), and N,N-dimethylformamide (5 mL) were used according to general procedure IV. The product was purified by flash chromatography
- 25 using 2% MeOH: 1% Et₃N: CHCl₃ as eluant to afford **208** (7.6 mg, 5%) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.18 (s, 1H), 8.85 (m, 2H), 8.30 (s, 1H), 8.12 (s, 1H), 7.66 (d, J= 7 Hz, 1H), 7.53 (m, 2H), 7.37 (m, 1H), 7.23 (d, J= 9 Hz, 1H), 4.75 (s, 2H), 2.12 (s, 3H). MS (ES): 501 (M+H)⁺.

30 **Example 90:**

168



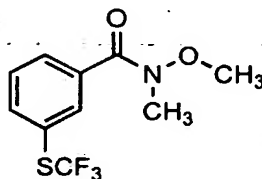
211

5

Step A:

212

3-(Trifluoromethylthio)benzoic acid (2.0 g, 9.0 mmol), oxalyl chloride (0.8 mL, 1.14 g, 9.0 mmol), methylene chloride (50 mL), and N,N-dimethylformamide (4 drops) were used according to general procedure V to provide **212** (2.0 g, 94%). The product was used in the next step without further purification or characterization.

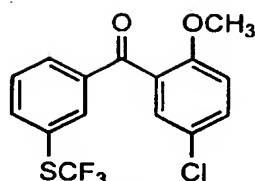
Step B:

213

Acid chloride **212** (2.0 g, 8.3 mmol), N,O-dimethylhydroxylamine hydrochloride (2.0 g, 20.5 mmol), Et₃N (2.4 mL, 1.7 g, 16.8 mmol), and CHCl₃ (40 mL) were used according to general procedure VII to provide **213** (1.6 g, 70%) as a clear oil. The product was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 7.87 (s, 1H), 7.79 (m, 2H), 7.60 (t, 1H), 3.50 (s, 3H), 3.24 (s, 3H).

Step C:

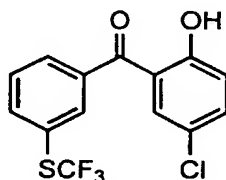
169



214

Amide 213 (0.8 g, 3.0 mmol), n-butyllithium (1.3 mL of a 2.5 M soln. in hexanes, 3.3 mmol), 2-bromo-4-chloroanisole (0.41 mL, 0.66 g, 3.0 mmol), and diethyl ether (10 mL) were used according to general procedure VIII. The product was purified by flash chromatography using 7:3 hexanes:ethyl acetate as eluant to afford 214 (0.56 g, 55%). ¹H NMR (400 MHz, DMSO-d₆) δ 7.97 (d, J= 8 Hz, 1H), 7.87 (m, 2H), 7.68 (d, J= 8 Hz, 1H), 7.60 (dd, J= 2.4, 8.8 Hz, 1H), 7.45 (d, J=2.8 Hz, 1H), 7.21 (d, J= 8.8 Hz, 1H), 3.62 (s, 3H).

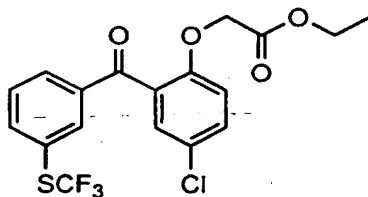
Step D:



215

Anisole 214 (0.56 g, 1.6 mmol), BBr₃ (2.0 mL of a 1.0 M soln. in CH₂Cl₂, 2.0 mmol), and CH₂Cl₂ (10 mL) were used according to general procedure IX to afford 215 (0.45 g, 86%). The product was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 10.42 (s, 1H), 7.95 (m, 2H), 7.87 (d, J= 8 Hz, 1H), 7.66 (t, J=8 Hz, 1H), 7.44 (dd, J=2.8, 8.8 Hz, 1H), 7.35 (d, J=2.8 Hz, 1H), 6.96 (d, J=8.8 Hz, 1H). MS (ES): 331 (M-H)⁻

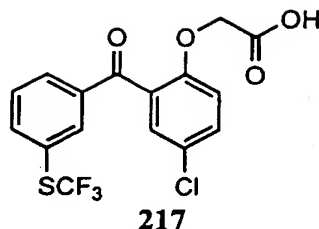
Step E:



216

Phenol 215 (0.45 g, 1.4 mmol), ethyl bromoacetate (0.17 mL, 0.25 g, 1.5 mmol), K₂CO₃ (0.48 g, 2.5 mmol), and acetone (20 mL) were used according to general procedure II to provide 216 (0.6 g, >100%) as a yellow oil. The product was used in the next step without further purification or characterization.

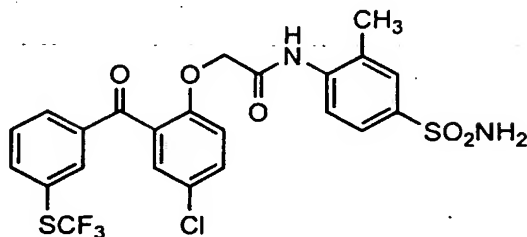
170

Step F:

Ester **216** (0.6 g, 1.4 mmol), LiOH (0.15 g, 3.64 mmol) and a solution of THF, EtOH, and water (15 mL) were used according to general procedure III. The resulting yellow oil was treated with hexanes to afford **217** (0.2 g, 36%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.13 (d, J = 7.6 Hz, 1H), 8.06 (s, 1H), 7.92 (d, J = 7.2 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.46 (dd, J = 2.8, 9.2 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 6.85 (d, J = 9.2 Hz, 1H), 3.96 (s, 2H). MS (ES): 389 (M-H).

Step G:

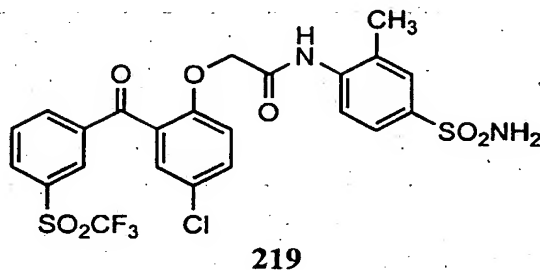
Acid **217** (50 mg, 0.13 mmol), HOBt (18 mg, 0.13 mmol), EDAC (25 mg, 0.13 mmol), aniline **399** (29 mg, 0.13 mmol), and N, N-dimethylformamide (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 5% MeOH:CHCl₃ as eluant and treated with several portions of hexanes to afford **211** (40 mg, 51%) as a beige solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.92 (s, 1H), 8.00 (s, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.94 (d, J = 1.2 Hz, 1H), 7.64 (m, 2H), 7.49 (d, J = 2.4 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 2.8 Hz, 1H), 6.75 (dd, J = 2.4, 8.8 Hz, 1H), 4.65 (s, 2H), 3.69 (m, 2H), 3.51 (m, 2H), 2.86 (m, 2H), 2.64 (m, 2H), 1.96 (s, 3H). MS (ES): 597 (M⁺), 596 (M-H).

Example 91

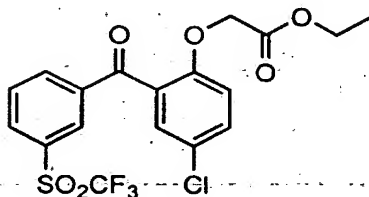
Acid **217** (70 mg, 0.18 mmol), oxalyl chloride (0.017 mL, 25 mg, 0.20 mmol), N, N-dimethylformamide (1 drop), and CH₂Cl₂ (7 mL) were used according to general

procedure V to afford the acid chloride. The acid chloride, aniline **466** (39 mg, 0.21 mmol), NaHCO_3 (84 mg, 1.0 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The resulting yellow solid was washed with minimal diethyl ether to afford **218** (50 mg, 45%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 9.44 (s, 1H), 8.38 (m, 3H), 8.01 (m, 1H), 7.70 (m, 5H), 7.31 (m, 3H), 4.80 (s, 2H), 2.16 (s, 3H). MS (ES): 559 (M^+).

Example 92

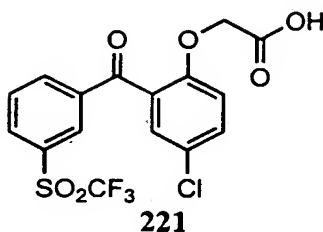


Step A:



To a round-bottom flask equipped with a stir bar, nitrogen on demand, and an addition funnel, were placed the ester **216** (0.56 g, 1.34 mmol) and CH_2Cl_2 (25 mL) and the reaction mixture was cooled to 0°C . A solution of m-chloroperoxybenzoic acid in CH_2Cl_2 (10 mL) was added dropwise via addition funnel and the resulting mixture was allowed to stir at 0°C for 0.5 h, after which time it was allowed to warm to rt and stir for an additional 16 h. When judged to be complete, the reaction was quenched with 10% sodium metabisulfite solution and extracted with CH_2Cl_2 . The organics were collected, washed with saturated NaHCO_3 , dried over MgSO_4 , filtered and the solvent was removed under reduced pressure to afford **220** (0.56 g, 93%) as a pale yellow oil. The product was used in the next reaction without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, $J = 8$ Hz, 1H), 8.29 (d, $J = 8$ Hz, 1H), 8.22 (s, 1H), 7.96 (t, $J = 7.6$ Hz, 1H), 7.62

(dd, $J = 2.8, 9.2$ Hz, 1H), 7.55 (d, $J = 2.8$ Hz, 1H), 7.17 (d, $J = 8.8$ Hz, 1H), 4.70 (s, 2H), 4.05 (m, 2H), 1.21 (m, 3H).

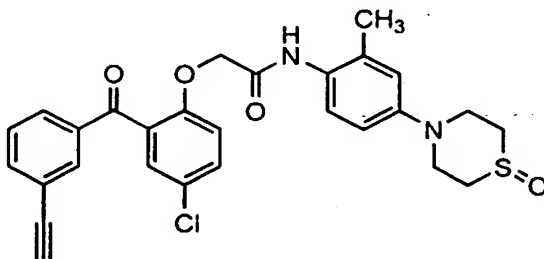
Step B:

Ester **220** (0.56 g, 1.2 mmol), LiOH (0.13g, 3.1 mmol) and a solution of THF, EtOH, and water (15 mL) were used according to general procedure III to afford **221** (0.1 g, 19%).

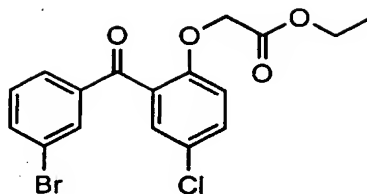
The product was used in the next step without further purification or characterization.

Step C:

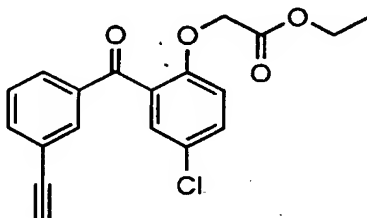
Acid **221** (100 mg, 0.24 mmol), oxalyl chloride (0.023 mL, 33 mg, 0.26 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **466** (41 mg, 0.22 mmol), NaHCO_3 (100 mg, 1.2 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH: CHCl_3 to afford **219** (72 mg, 51%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.34 (s, 1H), 8.01 (s, 1H), 7.96 (m, 2H), 7.61 (m, 6H), 7.49 (s, 1H), 7.23 (m, 2H), 4.76 (s, 2H), 2.12 (s, 3H).

Example 93**Step A:**

173

**223**

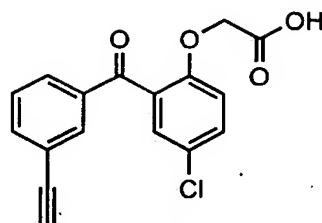
Phenol **432** (10 g, 0.032 mol), ethyl bromoacetate (3.5 mL, 5.3 g, 0.032 mol), K_2CO_3 (11 g, 0.080 mol), and acetone (120 mL) were used according to general procedure II to afford **223** (11.5 g, 91%) as a yellow oil. The product was used in the next step without further purification. 1H NMR (400 MHz, $DMSO-d_6$) δ 7.82 (m, 2H), 7.68 (d, J = 7.6 Hz, 1H), 7.53 (dd, J = 2.4, 8.8 Hz, 1H), 7.44 (m, 2H), 7.09 (d, J = 9.2 Hz, 1H), 4.74 (s, 2H), 4.04 (q, J = 7.2 Hz, 2H), 1.13 (m, 3H).

Step B:**224**

To a round-bottom flask equipped with a stir bar and nitrogen on demand were added the ester **223** (1.5 g, 3.8 mmol), trimethylsilylacetylene (0.6 mL, 0.4 g, 4.1 mmol), tetrakis(triphenylphosphine)palladium (0) (0.31 g, 0.27 mmol), copper(I) iodide (0.15 g, 0.80 mmol), triethylamine (1.7 mL, 1.2 g, 0.80 mmol), and N,N -dimethylformamide (15 mL) and the reaction was allowed to stir at 80 °C for 18h. When judged to be complete, the reaction mixture was poured into ethyl acetate and water. The organics were collected, washed with water and brine, dried over Na_2SO_4 , filtered through a pad of celite, and the solvents were removed under reduced pressure. To the resulting residue was added tetrahydrofuran (20 mL) and tetrabutylammonium fluoride (3 mL). The mixture was allowed to stir at RT for 10 min, after which it was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, dried over Na_2SO_4 , filtered, and the solvents were removed under reduced pressure. The resulting product was purified by flash chromatography using 7:3 hexanes:ethyl acetate to provide **224** (0.69 g, 53%). 1H NMR (400 MHz, $DMSO-d_6$) δ 7.73 (m, 2H), 7.54 (m, 2H), 7.44 (s, 1H), 7.34

(m, 1H), 7.09 (d, $J = 9.2$ Hz, 1H), 4.74 (s, 2H), 4.04 (m, 2H), 1.11 (m, 3H). MS (ES): 343 (M^+).

Step C:



225

Ester **224** (0.69 g, 2.0 mmol), LiOH (0.2 g, 5.0 mmol) and a solution of THF, EtOH, and water (12 mL) were used according to general procedure III to afford **225** (0.37 g, 59%).

^1H NMR (400 MHz, DMSO- d_6) δ 13.30 (bs, 1H), 7.86 (s, 1H), 7.73 (m, 2H), 7.54 (m, 2H), 4.62 (s, 2H), 4.25 (s, 1H).

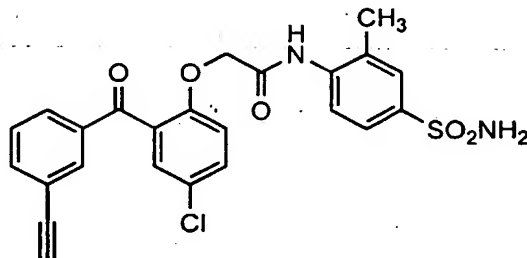
Step D:

Acid **225** (75 mg, 0.24 mmol), HOBt (32 mg, 0.24 mmol), EDAC (46 mg, 0.24 mmol), aniline **399** (53 mg, 0.24 mmol), and N, N-dimethylformamide (5 mL) were used

according to general procedure IV. The product was purified by flash chromatography using 5% MeOH:CHCl₃ as eluant and treated with several portions of hexanes to afford

222 (17 mg, 14%) as a pale yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.86 (s, 1H), 7.75 (m, 2H), 7.70 (d, $J = 7.6$ Hz, 1H), 7.60 (dd, $J = 2.8, 9.2$ Hz, 1H), 7.49 (t, $J = 8$ Hz, 1H), 7.45 (d, $J = 2.8$ Hz, 1H), 7.21 (d, $J = 9.2$ Hz, 1H), 7.09 (d, $J = 8.8$ Hz, 1H), 6.81 (s, 1H), 6.75 (m, 1H), 4.66 (s, 2H), 4.28 (s, 1H), 3.69 (m, 2H), 3.52 (m, 2H), 2.86 (m, 2H), 2.63 (m, 2H), 1.96 (s, 3H). MS (ES): 521 (M^+).

Example 94

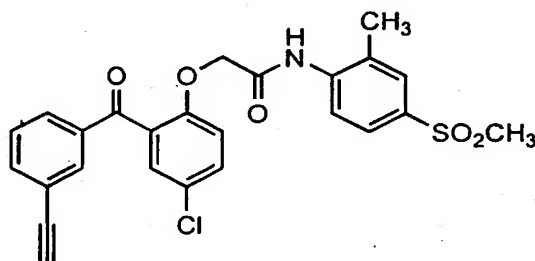


226

Step A:

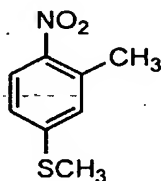
Acid 225 (80 mg, 0.25 mmol), oxalyl chloride (0.024 mL, 35 mg, 0.28 mmol), N,N-dimethylformamide (1 drop), and CH₂Cl₂ (3 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline 466 (48 mg, 0.26 mmol), NaHCO₃ (105 mg, 1.3 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:CHCl₃ to afford 226 (20 mg, 16%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.30 (s, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.58 (m, 4H), 7.45 (m, 2H), 7.22 (m, 3H), 4.77 (s, 2H), 4.27 (s, 1H), 2.13 (s, 3H). MS ES): 482 (M⁺), 481 (M-H)⁻.

Example 95



227

Step A:

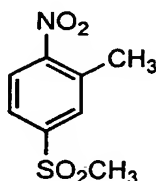


228

To a round-bottom flask equipped with a stir bar and nitrogen on demand was added 5-fluoro-2-nitrotoluene (2.4 mL, 3.0 g, 0.019 mol), sodium thiomethoxide (1.5 g, 0.021 mol), and N,N-dimethylformamide (50 mL). The reaction was allowed to stir at 85 °C for 2-4 h, after which time the reaction mixture was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, washed with water, dried over Na₂SO₄, treated with activated carbon, filtered through celite and the solvents were removed under reduced pressure to afford 228 (2.95 g, 85%) as an orange oil. The product

was used in the next step without further purification. ^1H NMR (400 MHz, DMSO- d_6) δ 7.92 (s, 1H), 7.29 (d, J = 1.6 Hz, 1H), 7.24 (dd, J = 2, 8.4 Hz, 1H), 2.52 (s, 3H), 2.50 (s, 3H).

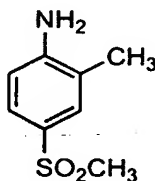
5 **Step B:**



229

To a round-bottom flask equipped with a stir bar and nitrogen on demand was added 228 (2.95 g, 0.016 mol) and CH_2Cl_2 (50 mL). The reaction was cooled to 0°C and a solution
10 of m-chloroperoxybenzoic acid (5.8 g, 0.033 mol) in CH_2Cl_2 (10 mL) was added dropwise via addition funnel. The resulting mixture was allowed to stir at 0°C for 0.5 h, after which time it was allowed to warm to RT and stir for an additional 3-4h. When judged to be complete, the reaction was quenched with 10% sodium metabisulfite solution and extracted with CH_2Cl_2 . The organics were collected, washed with saturated NaHCO_3 ,
15 dried over MgSO_4 , filtered and the solvent was removed under reduced pressure to afford 229 (3.0 g, 88%) as yellow solid. The product was used in the next reaction without further purification. ^1H NMR (400 MHz, CDCl_3) δ 8.06 (d, J = 8.4 Hz, 1H), 7.92 (m, 2H), 3.08 (s, 3H), 2.65 (s, 3H).

20 **Step C:**



230

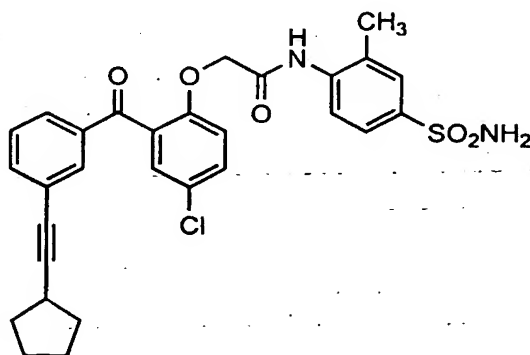
To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative
25 229 (1.5 g, 6.9 mmol), toluene (50 mL), and palladium on charcoal (0.15 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 50 p.s.i. for 7 h. When judged to be complete, the reaction was filtered through a celite plug and the

solvents were removed under reduced pressure to provide a crystalline material. The residue was washed several times with diethyl ether to afford **230** (1.3 g, >99%). ¹H NMR (400 MHz, DMSO-d₆) δ 7.36 (m, 2H), 6.65 (d, J= 8.4 Hz, 1H), 5.81 (s, 2H), 2.98 (s, 3H), 2.06 (s, 3H).

Step D:

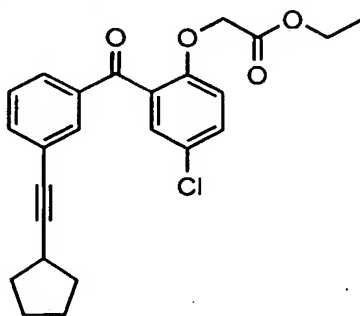
Acid **225** (107 mg, 0.34 mmol), oxalyl chloride (0.032mL, 47mg, 0.37 mmol), N, N-dimethylformamide (1 drop), and CH₂Cl₂ (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **230** (63 mg, 0.34 mmol), NaHCO₃ (143 mg, 1.7 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:CHCl₃ to afford **227** (8 mg, 5%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.34 (s, 1H), 7.73 (m, 6H), 7.60 (dd, J= 2.8, 8.8 Hz, 1H), 7.50 (t, J= 8 Hz, 1H), 7.46 (d, J= 2.4 Hz, 1H), 7.21 (d, J= 8.8 Hz, 1H), 4.79 (s, 2H), 4.29 (s, 1H), 3.27 (s, 3H), 2.18 (s, 3H). MS ES): 481 (M-H)⁻.

Example 96



231

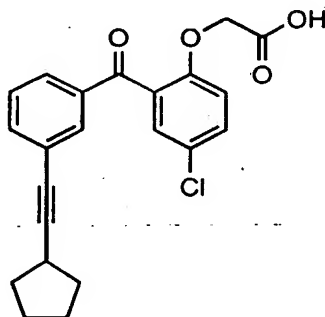
Step A:



178

232

To a round-bottom flask equipped with a stir bar and nitrogen on demand were added the ester **223** (0.2 g, 0.5 mmol), cyclopentylacetylene (52 mg, 0.55 mmol), tetrakis(triphenylphosphine)palladium (0) (40 mg, 0.035 mmol), copper(I) iodide (20 mg, 0.11 mmol), triethylamine (0.22 mL, 0.16 g, 1.6 mmol), and N,N-dimethylformamide (5 mL) and the reaction was allowed to stir at 80 °C for 18h. When judged to be complete, the reaction mixture was poured into ethyl acetate and water. The organics were collected, washed with water, dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 8:2 hexanes: ethyl acetate to afford **232** (130 mg, 63%) as an orange oil. ¹H NMR (300 MHz, DMSO-d₆) δ 7.68 (m, 3H), 7.59 (dd, J = 2.7, 9 Hz, 1H), 7.48 (m, 2H), 7.13 (d, J = 9 Hz, 1H), 4.79 (s, 2H), 4.10 (m, 2H), 2.88 (m, 1H), 2.00 (m, 2H), 1.63 (m, 6H), 1.17 (m, 3H).

Step B:**233**

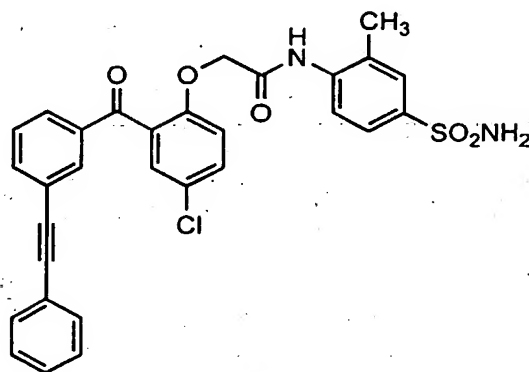
Ester **232** (0.13 g, 0.32 mmol), LiOH (33 mg, 0.79 mmol) and a solution of THF, EtOH, and water (8 mL) were used according to general procedure III to afford **233** (0.15 g, >99%). The product was used in the next step without further purification or characterization.

Step C:

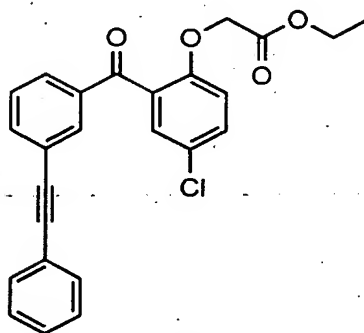
Acid **233** (140 mg, 0.37 mmol), oxalyl chloride (0.033 mL, 48 mg, 0.38 mmol), N,N-dimethylformamide (1 drop), and CH₂Cl₂ (5 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **466** (73 mg, 0.39 mmol), NaHCO₃ (155 mg, 1.85 mmol), acetone (7 mL), and water (0.5 mL) were used

according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:CHCl₃ to afford **231** (88 mg, 43%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.28 (s, 1H), 7.61 (m, 8H), 7.44 (m, 2H), 7.21 (m, 2H), 4.77 (s, 2H), 2.81 (m, 1H), 2.14 (s, 3H), 1.93 (m, 2H), 1.58 (m, 6H).

Example 97

**234**

Step A:

**235**

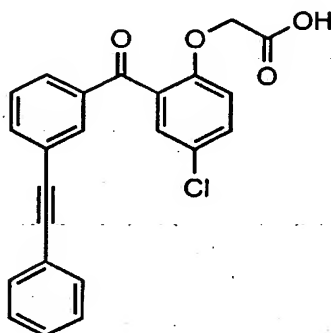
To a round-bottom flask equipped with a stir bar and nitrogen on demand were added the ester **223** (0.2 g, 0.5 mmol), phenylacetylene (52 mg, 0.55 mmol),

tetrakis(triphenylphosphine)palladium (40 mg, 0.035 mmol), copper(I) iodide (20 mg, 0.11 mmol), triethylamine (0.22 mL, 0.16 g, 1.6 mmol), and N,N-dimethylformamide (5 mL) and the reaction was allowed to stir at 80 °C for 18 h. When judged to be complete, the reaction mixture was poured into ethyl acetate and water. The organics were collected, washed with water, dried over Na₂SO₄, filtered, and the solvents were removed under

reduced pressure. The product was purified by flash chromatography using 8:2 hexanes:ethyl acetate to afford **235** (150 mg, 72%) as a green oil. ¹H NMR (300 MHz,

180

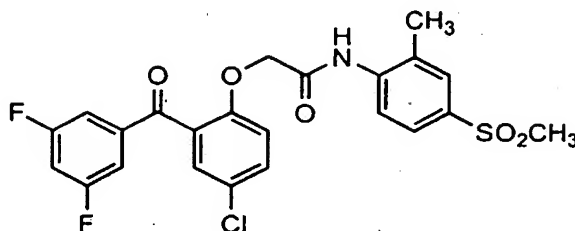
DMSO- d_6 δ 7.87 (d, J = 4.8 Hz, 1H), 7.82 (m, 2H), 7.60 (m, 4H), 7.50 (d, J = 3 Hz, 1H), 7.46 (m, 3H), 7.15 (d, J = 9 Hz, 1H), 4.82 (s, 2H), 4.10 (m, 2H), 1.21 (m, 3H).

Step B:**236**

Ester **235** (0.15 g, 0.36 mmol), LiOH (38 mg, 0.90 mmol) and a solution of THF, EtOH, and water (8 mL) were used according to general procedure III to afford **236** (64 mg, 46%). The product was used in the next step without further purification or characterization.

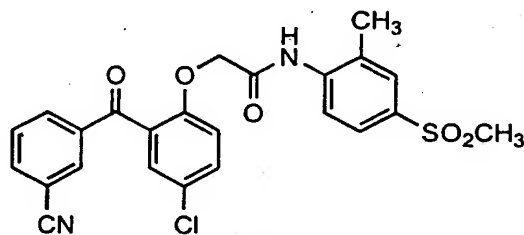
Step C:

Acid **236** (64 mg, 0.16 mmol), oxalyl chloride (0.015 mL, 23 mg, 0.17 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (5 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **466** (31 mg, 0.17 mmol), NaHCO_3 (67 mg, 0.8 mmol), acetone (5 mL), and water (0.5 mL) were used according to general procedure VI. The product was filtered through a pad of silica gel to afford **234** (10 mg, 11%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.34 (s, 1H), 7.90 (s, 1H), 7.79 (m, 2H), 7.62 (m, 3H), 7.54 (m, 4H), 7.47 (d, J = 3 Hz, 1H), 7.38 (m, 3H), 7.22 (m, 3H), 4.80 (s, 2H), 2.15 (s, 3H).

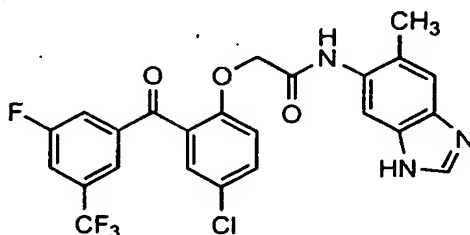
Example 98**237**

Step A:

Acid 49 (120 mg, 0.37 mmol), oxalyl chloride (0.035 mL, 50 mg, 0.40 mmol), N,N-dimethylformamide (1 drop), and CH₂Cl₂ (7 mL) were used according to general
 5 procedure V to afford the acid chloride. The acid chloride, aniline 230 (69 mg, 0.37 mmol), NaHCO₃ (155 mg, 1.85 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The resulting yellow oil was treated with pentanes to afford 237 (39 mg, 21%) as a pale yellow solid. ¹H NMR (300 MHz, DMSO-d₆) δ 9.51 (s, 1H), 7.66 (m, 5H), 7.53 (d, J = 2.7 Hz, 1H), 7.49 (m, 2H), 7.25 (d, J = 9 Hz, 1H), 4.87 (s, 2H), 3.20 (s, 3H), 2.26 (s, 3H). MS (ES): 494 (M⁺).

Example 99**238**

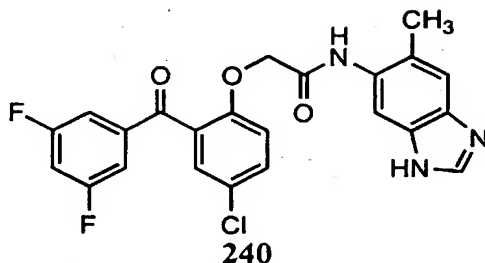
15 Acid 129 (120 mg, 0.38 mmol), oxalyl chloride (0.037 mL, 53 mg, 0.42 mmol), N,N-dimethylformamide (1 drop), and CH₂Cl₂ (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline 230 (70 mg, 0.38 mmol), NaHCO₃ (160 mg, 1.9 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The product purified by flash chromatography using
 20 5% MeOH:CHCl₃ to afford 238 (18 mg, 10%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.42 (s, 1H), 8.16 (s, 1H), 8.06 (m, 2H), 7.67 (m, 2H), 7.49 (d, J = 2.8 Hz, 1H), 7.21 (d, J = 9.2 Hz, 1H), 4.80 (s, 2H), 3.14 (s, 3H), 2.18 (s, 3H). MS (ES): 481 (M-H)

Example 100**239**

Acid **71** (300 mg, 0.8 mmol), HOBt (108 mg, 0.8 mmol), EDAC (153 mg, 0.8 mmol), aniline **210** (118 mg, 0.8 mmol), and N,N-dimethylformamide (7 mL) were used according to general procedure IV. The product was purified by flash chromatography using 3% MeOH: 1% Et₃N: CH₂Cl₂ as eluant to afford **239** (60 mg, 15%) as a white solid.

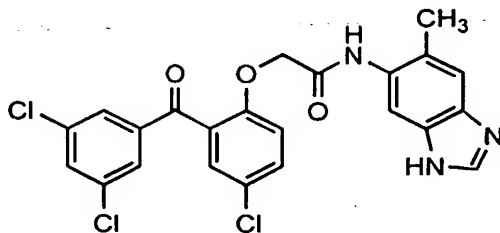
At ambient temp. the product exists as a mixture of tautomers. ¹H NMR (400 MHz, DMSO-d₆) δ 12.27 (m, 1H), 9.15 (m, 1H), 8.00 (s, 1H), 7.99 (d, J= 8 Hz, 1H), 7.87 (m, 2H), 7.66 (d, J= 9 Hz, 1H), 7.45 (m, 3H), 4.74 (s, 2H), 2.12 (m, 3H). MS (ES): 506 (M⁺), 507 (M+H)⁺.

Example 101



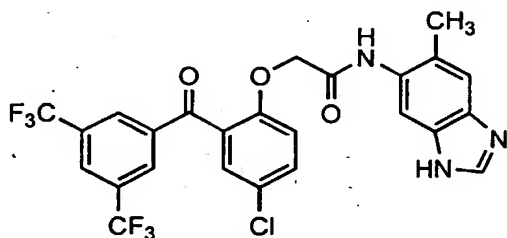
Acid **49** (120 mg, 0.37 mmol), oxalyl chloride (0.035 mL, 50mg, 0.40 mmol), N,N-dimethylformamide (1 drop), and CH₂Cl₂ (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **210** (54 mg, 0.37 mmol), NaHCO₃ (155 mg, 1.9 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The product purified by flash chromatography using 5% MeOH:CHCl₃ to afford **240** (22 mg, 13%) as a pale yellow solid. At ambient temperature the product exists as a mixture of tautomers. ¹H NMR (400 MHz, DMSO-d₆) δ 12.26 (m, 1H), 9.14 (m, 1H), 8.09 (s, 1H), 7.64 (d, J= 9 Hz, 1H), 7.50 (m, 4H), 7.23 (m, 2H), 4.75 (m, 2H), 2.12 (m, 3H). MS (ES): 456 (M⁺), 457 (M+H)⁺, 455(M-H)⁻.

Example 102



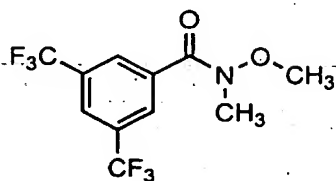
Acid 76 (120 mg, 0.33 mmol), oxalyl chloride (0.032 mL, 46 mg, 0.37 mmol), N, N-dimethylformamide (1 drop), and CH₂Cl₂ (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline 210 (51 mg, 0.35 mmol), NaHCO₃ (139 mg, 1.7 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The product purified by flash chromatography using 2% MeOH:CH₂Cl₂ to afford 241 (11 mg, 7%) as a white solid. At ambient temperature the product exists as a mixture of tautomers. ¹H NMR (400 MHz, DMSO-d₆) δ 12.26 (s, 1H), 9.15 (m, 1H), 8.09 (s, 1H), 7.87 (m, 1H), 7.70 (m, 2H), 7.64 (m, 1H), 7.55 (m, 2H), 7.21 (m, 1H), 4.75 (m, 2H), 2.12 (m, 3H). MS (ES): 490 (M+H)⁺, 488 (M-H)⁻.

Example 103



242

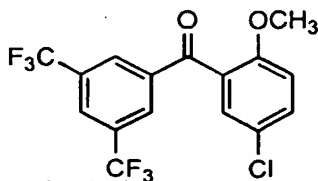
Step A:



243

3,5-Bis(trifluoromethyl)benzoyl chloride (5.0 g, 0.018 mol), N,O-dimethylhydroxylamine hydrochloride (3.5 g, 0.036 mol), Et₃N (7.5 mL, 5.5 g, 0.054 mol), and CH₂Cl₂ (50 mL) were used according to general procedure VII to provide 243 (5.0 g, 92%) as a clear oil. The product was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 8.24 (s, 1H), 8.22 (s, 2H), 3.52 (s, 3H), 3.28 (s, 3H).

Step B:

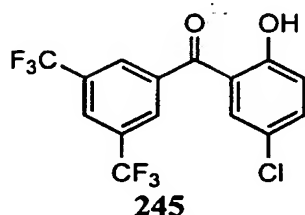


244

Amide 243 (5.0 g, 0.017 mol), n-butyllithium (11.4 mL of a 1.6 M solution in hexanes, 0.018 mol), 2-bromo-4-chloroanisole (2.3 mL, 3.8 g, 0.017 mol), and diethyl ether (60 mL) were used according to general procedure VIII. The product was purified by flash chromatography using 85:15 hexanes:ethyl acetate as eluant to afford 244 (3.76 g, 58%).

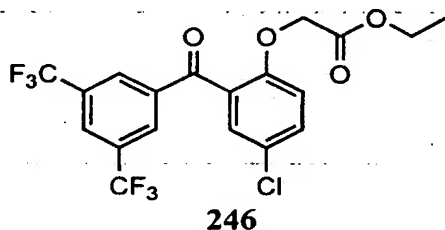
¹H NMR (400 MHz, DMSO-d₆) δ 8.43 (s, 1H), 8.18 (s, 2H), 7.65 (t, J= 2.8 Hz, 1H), 7.52 (d, J= 2.8 Hz, 1H), 7.24 (d, J= 8.8 Hz, 1H), 3.61 (s, 3H).

Step C:



Anisole 244 (3.76 g, 9.8 mmol), BBr₃ (29 mL of a 1.0 M soln. in CH₂Cl₂, 29 mmol), and CH₂Cl₂ (80 mL) were used according to general procedure IX to afford 245 (3.2 g, 89%) a pale green solid. The product was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 10.6 (s, 1H), 8.40 (s, 1H), 8.21 (s, 2H), 7.48 (m, 2H), 6.98 (d, J= 8.8 Hz, 1H).

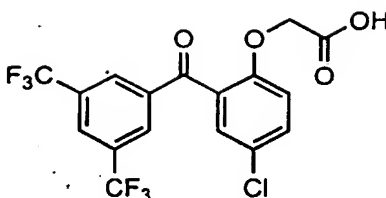
Step D:



Phenol 245 (3.2 g, 8.7 mmol), ethyl bromoacetate (1.1 mL, 1.6 g, 9.5 mmol), K₂CO₃ (3.0 g, 21.7 mmol), and acetone (50 mL) were used according to general procedure II to provide 246 (3.8 g, 97%) as a pale yellow solid. The product was used in the next step without further purification. ¹H NMR (300 MHz, DMSO-d₆) δ 8.47 (s, 1H), 8.31 (s, 2H), 7.68 (dd, J= 3, 9 Hz, 1H), 7.61 (d, J= 2.4 Hz, 1H), 7.21 (d, J= 9 Hz, 1H), 4.79 (s, 2H), 4.06 (q, J= 7 Hz, 2H), 1.13 (t, J= 7 Hz, 3H).

Step E:

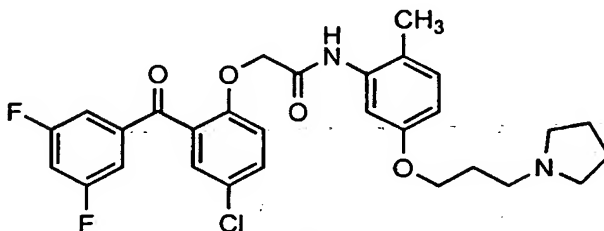
185

**247**

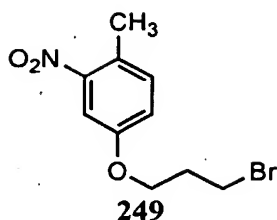
Ester **246** (3.8 g, 8.4 mmol), LiOH (0.88 g, 20.9 mmol) and a solution of THF, EtOH, and water (25 mL) were used according to general procedure III. The resulting white foam was treated with diethyl ether to afford **247** (3.1 g, 86%) as a white solid. ¹H NMR (300 MHz, DMSO-d₆) δ 8.44 (s, 1H), 8.34 (s, 2H), 7.67 (dd, J= 3, 9 Hz, 1H), 7.58 (d, J= 3 Hz, 1H), 7.16 (d, J= 9 Hz, 1H), 4.63 (s, 2H).

Step F:

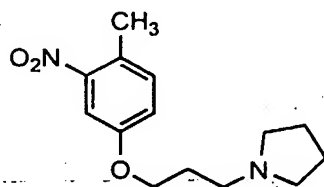
Acid **247** (150 mg, 0.35 mmol), HOBt (47 mg, 0.35 mmol), EDAC (67 mg, 0.35 mmol), aniline **210** (52 mg, 0.35 mmol), and N,N-dimethylformamide (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 3% MeOH:CHCl₃ as eluant to afford **242** (9 mg, 5%) as a white solid. At ambient temperature, the product exists as a mixture of tautomers. ¹H NMR (300 MHz, DMSO-d₆) δ 12.32 (s, 1H), 9.20 (s, 1H), 8.44 (s, 1H), 8.35 (m, 2H), 8.14 (m, 1H), 7.76 (m, 1H), 7.62 (m, 1H), 7.51 (s, 1H), 7.30 (d, J= 9 Hz, 1H), 4.77 (s, 2H), 2.13 (s, 3H). MS (ES): 556 (M⁺), 557 (M-H)⁻.

Example 104**248****Step A:**

186



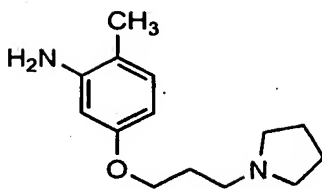
Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 3-methyl-4-nitrophenol (2.0 g, 0.013 mol), dibromopropane (10.6 mL, 21.0 g, 0.10 mol),
5 potassium carbonate (2.7 g, 0.02 mol), and N, N-dimethylformamide (50 mL) and the mixture was allowed to stir at rt for 18 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing CH₂Cl₂ and water. The organics were collected, washed with 0.5 N NaOH soln., dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The resulting red oil was distilled to afford 249
10 (2.46 g, 69%). ¹H NMR (400 MHz, DMSO-d₆) δ 7.49 (d, J= 2.4 Hz, 1H), 7.37 (d, J= 8.4 Hz, 1H), 7.21 (dd, J= 2.4, 8.4 Hz, 1H), 4.11 (t, J= 6 Hz, 2H), 3.63 (t, J= 6 Hz, 2H), 2.38 (s, 3H), 2.22 (m, 2H).

Step B:

15 Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 249 (1.5 g, 5.47 mmol), pyrrolidine (0.91 mL, 0.78 g, 10.9 mmol), potassium carbonate (1.1 g, 8.2 mmol), and N, N-dimethylformamide (30 mL) and the mixture was allowed to
20 stir at rt for 4 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to afford 250 (1.24 g, 89%) as a brown oil. The product was used in the next step without further purification or characterization.

Step C:

187

**251**

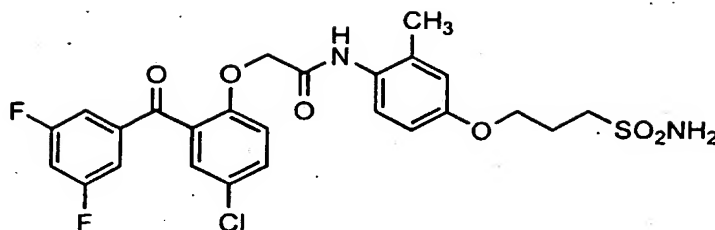
To a plastic-coated reaction vessel equipped with a stir bar, was added compound **250** (1.3 g, 4.9 mmol), absolute ethanol (20 mL), and palladium on charcoal (0.13 g of 10% Pd/C, 10% w/w). The vessel was placed on a hydrogenation apparatus at 60 p.s.i. for 3 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide a dark oil. The residue was treated with a small amount of ethyl acetate and hexanes and the resulting precipitate was filtered and the mother liquor was concentrated under reduced pressure to afford **251** (1.0 g, 87%), as an orange solid. ¹H NMR (400 MHz, DMSO-d₆) δ 6.72 (d, J= 8.4 Hz, 1H), 6.14 (d, J= 2.4 Hz, 1H), 5.98 (dd, J= 2.4, 8.4 Hz, 1H), 4.73 (s, 2H), 3.82 (t, J= 6.4 Hz, 2H), 2.46 (m, 2H), 2.37 (m, 4H), 1.92 (s, 3H), 1.77 (m, 2H), 1.63 (m, 4H).

Step D:

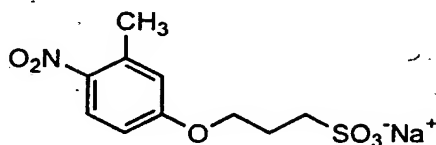
Acid **49** (120 mg, 0.37 mmol), oxalyl chloride (0.035 mL, 50 mg, 0.40 mmol), N,N-dimethylformamide (1 drop), and CH₂Cl₂ (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **251** (87 mg, 0.37 mmol), NaHCO₃ (155 mg, 1.85 mmol), acetone (8 mL), and water (0.5 mL) were used according to general procedure VI. The resulting yellow oil was treated with pentanes to afford **248** (92 mg, 46%) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.08 (s, 1H), 7.62 (dd, J= 2.8, 8.8 Hz, 1H), 7.55 (t, J= 9.2 Hz, 1H), 7.47 (d, J= 2.4 Hz, 1H), 7.42 (m, 2H), 7.19 (d, J= 8.8 Hz, 1H), 7.01 (m, 2H), 6.63 (d, J= 8.4 Hz, 1H), 4.74 (s, 2H), 3.89 (t, J= 6.4 Hz, 2H), 2.45 (m, 2H), 2.39 (bs, 4H), 1.98 (s, 3H), 1.81 (t, J= 6.8 Hz, 2H), 1.63 (s, 4H). MS(ES): 543 (M⁺).

Example 105

188

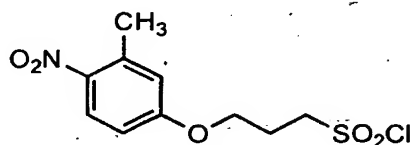


252

Step A:

253

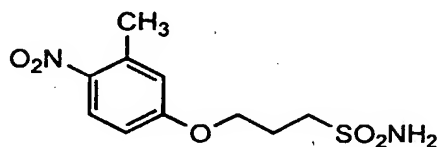
To a round-bottom flask equipped with an overhead stirrer, and addition funnel, and nitrogen on demand was placed sodium hydride (7.8 g of 60% by weight in mineral oil, 0.20 mol) and anhydrous tetrahydrofuran (THF, 300 mL). The mixture was cooled to 0 °C and 2-methyl-3-nitrophenol (30 g, 0.20 mol) was added dropwise as a solution in THF (100 mL). The reaction was then allowed to warm to rt, heated to 40 °C for 15 min., and then allowed to cool to rt. At this time, 1,3-propane sultone (25.6 g, 0.21 mol) in THF (100 mL) was added dropwise and the reaction was heated to reflux for 4-6 h. When judged to be complete, the reaction mixture was filtered and the resulting solid was washed with absolute ethanol and diethyl ether and dried in a vacuum oven. A solid precipitated out of the mother liquor, was filtered and washed with absolute ethanol and diethyl ether and dried in a vacuum oven to afford **253** (27 g, 46%) of a pale yellow solid. ¹H-NMR (300 MHz, DMSO-d₆) δ 8.06 (d, J = 9 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 6.98 (dd, J = 2.7, 9.3 Hz, 1H), 4.22 (t, J = 6.6 Hz, 2H), 2.58 (m, 2H), 2.52 (s, 3H), 2.04 (m, 2H).

Step B:

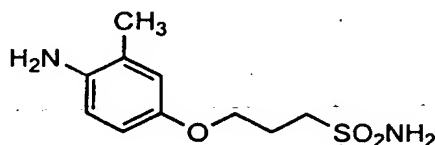
254

To a round-bottom flask equipped with a stir bar, an addition funnel, and nitrogen on demand was added the sulfonic acid salt **253** (11 g, 0.037 mol) and N,N-dimethylformamide (250 mL) and the reaction was cooled to 0 °C. Thionyl chloride (8.0

mL, 13.0 g, 0.11 mol) was added dropwise and the resulting mixture was allowed to stir at 0 °C for 0.5 h, after which time it was allowed to warm to rt and stir for an additional 3 h. When judged to be complete, the reaction mixture was poured into a beaker of ice and the resulting white precipitate was filtered and placed in a vacuum oven to afford **254** (8.7 g, 80%) as a white solid. ¹H NMR (300 MHz, DMSO-d₆) δ 8.06 (d, J= 9 Hz, 1H), 7.05 (d, J= 2.7 Hz, 1H), 6.98 (dd, J= 2.7, 9.3 Hz, 1H), 4.22 (t, J= 6.3 Hz, 2H), 2.61 (m, 2H), 2.57 (s, 3H), 2.04 (m, 2H).

Step C:**255**

To a round-bottom flask equipped with a stir bar, an addition funnel, and nitrogen on demand was added ammonium hydroxide (10 mL) and THF (20 mL) and the reaction was cooled to 0 °C. Sulfonyl chloride **254** (2 g, 6.8 mmol) was added dropwise and the reaction was allowed to stir at 0 °C for 15 min, after which time the reaction was poured into a beaker of ice and extracted with ethyl acetate. The organics were collected, washed with water, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to provide **255** (1.4 g, 77%) as a white solid. ¹H NMR (300 MHz, DMSO-d₆) δ 8.07 (d, J= 9 Hz, 1H), 7.06 (d, J= 2.7 Hz, 1H), 7.00 (dd, J= 2.7, 9 Hz, 1H), 6.91 (s, 2H), 4.24 (t, J= 6 Hz, 2H), 3.16 (t, J= 7.5 Hz, 2H), 2.56 (s, 3H), 2.18 (m, 2H).

Step D:**256**

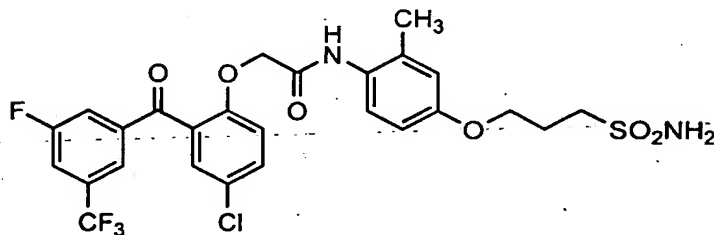
To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **255** (0.29 g, 1.1 mmol), absolute ethanol (25 mL), and palladium on charcoal (29 mg of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 60 p.s.i. for 2-4 h. When judged to be complete, the reaction was filtered through a celite

plug and the solvents were removed under reduced pressure to provide **256** (0.25 g, 98%) as a pale brown solid. ^1H NMR (400 MHz, DMSO- d_6) δ 6.80 (s, 2H), 6.54 (s, 1H), 6.49 (s, 2H), 4.34 (s, 2H), 3.89 (t, J = 6 Hz, 2H), 2.58 (m, 2H), 3.05 (m, 2H), 1.99 (m, 5H).

5 Step E:

Acid **49** (120 mg, 0.37 mmol), oxalyl chloride (0.035 mL, 50 mg, 0.40 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **256** (81 mg, 0.33 mmol), NaHCO_3 (155 mg, 1.85 mmol), acetone (8 mL), and water (0.5 mL) were used according to general procedure VI to afford **252** (103 mg, 50%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.09 (s, 1H), 7.62 (dd, J = 2.8, 9.2 Hz, 1H), 7.55 (m, 1H), 7.47 (d, J = 2.8 Hz, 1H), 7.41 (m, 2H), 7.19 (d, J = 9.2 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.83 (s, 2H), 6.76 (d, J = 2.8 Hz, 1H), 6.69 (dd, J = 2.8, 8.4 Hz), 4.70 (s, 2H), 4.01 (t, J = 6.4 Hz, 2H), 3.08 (t, J = 8 Hz, 2H), 2.07 (m, 2H), 2.00 (s, 3H). MS (ES): 553 (M^+).

Example 106

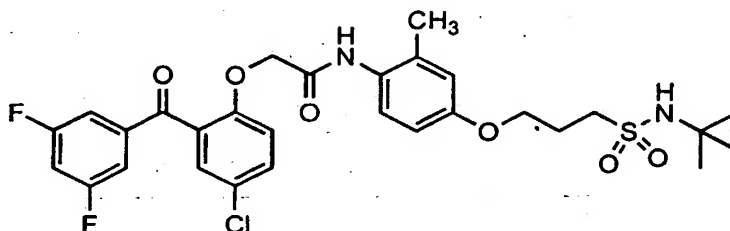


20 **257**

Acid **71** (13 g, 0.035 mol), oxalyl chloride (7.0 mL, 9.8 g, 0.077 mol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (100 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **256** (7.81 g, 0.032 mol), NaHCO_3 (15 g, 0.18 mol), acetone (125 mL), and water (10 mL) were used according to general procedure VI. The product was crystallized from methanol to afford **257** (10.5 g, 50%) as a white solid. ^1H NMR (300 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.90 (m, 2H), 7.71 (dd, J = 2.7, 9 Hz, 1H), 7.57 (d, J = 2.7 Hz, 1H), 7.25 (d, J = 9 Hz, 1H), 7.13 (d, J = 9 Hz, 1H), 6.88 (s, 2H), 6.80 (d, J = 2.7 Hz, 1H), 6.73 (dd, J = 2.7, 9 Hz, 1H), 4.74 (s, 2H), 4.07 (t, J = 6 Hz, 2H), 3.13 (m, 2H), 2.13 (m, 2H), 2.03 (s, 3H).

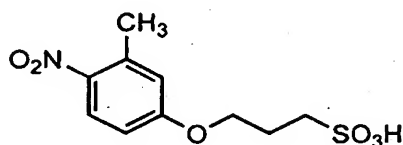
MS (ES): 602 (M-H)⁻, 603 (M)⁺. Anal. Calcd for C₂₆H₂₃N₂O₆ClF₄S: C, 51.79; H, 3.84; N, 4.65. Found: C, 51.91; H, 3.88; N, 4.66.

5 **Example 107**



258

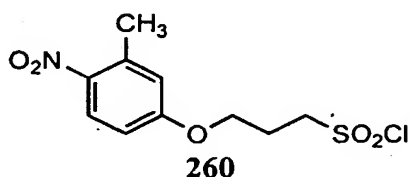
Step A:



259

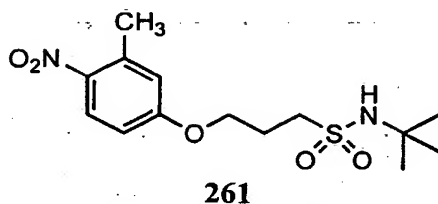
To a round-bottom flask equipped with a stir bar, and nitrogen on demand were placed 2-methyl-3-nitrophenol (10 g, 0.065 mol), acetone (100 mL), potassium carbonate (27 g, 0.20 mol), and 1,3-propane sultone (6.0 mL, 8.3 g, 0.068 mol). The mixture was heated to reflux for 1 h, after which time it was allowed to cool to rt and stir for an additional 72 h. When judged to be complete, the reaction mixture was concentrated under reduced pressure. The resulting yellow residue was dissolved in a minimal amount of water, acidified to pH 2 using conc. HCl, and extracted with a mixture of absolute ethanol/ethyl acetate. The organics were collected, dried over MgSO₄, filtered and the solvents removed under reduced pressure to afford 259 (10.2 g, 57%) of a pale yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.00 (d, J= 9.2 Hz, 1H), 6.99 (d, J= 2.4 Hz, 1H), 6.92 (dd, J= 2.4, 8.8 Hz, 1H), 4.16 (t, J= 6.4 Hz, 2H), 2.47 (m, 5H), 1.98 (m, 2H).

25 **Step B:**

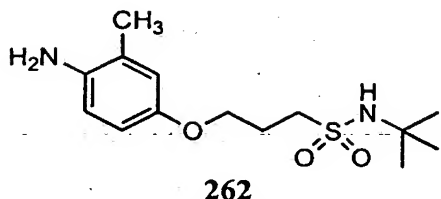


260

To a round-bottom flask equipped with a stir bar, reflux condensor, and nitrogen on demand were added the sulfonic acid **259** (3 g, 0.011 mol) and phosphorus oxychloride (POCl_3 , 100 mL). The reaction was heated to reflux for 18 h, after which time it continued to stir at rt for 24 h. The mixture was filtered and the POCl_3 was removed under reduced pressure to afford **260** (3.8 g, >100%) as a brown oil. The product was used in the next step without further purification or characterization.

Step C:

To a round-bottom flask equipped with a stir bar and nitrogen on demand was added t-butylamine (0.33 mL, 0.23 g, 3.1 mmol), triethylamine (0.72 mL, 0.52 g, 5.2 mmol), and chloroform (20 mL). Sulfonyl chloride **260** (0.76 g, 2.6 mmol) in chloroform (3 mL) was added dropwise and the reaction was allowed to stir at rt for 2 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing CHCl_3 and water, the organics were collected, washed with brine, dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. The resulting brown residue was filtered through a pad of silica gel, eluting with hexanes to provide **261** (0.37 g, 43%) as a white solid. The product was used in the next step without further purification or characterization.

Step D:

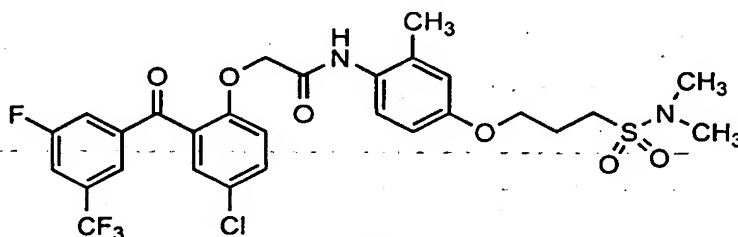
To a plastic-coated reaction vessel equipped with a stir bar, were added compound **261** (0.37 g, 1.1 mmol), ethanol (20 mL), and palladium on charcoal (37 mg of 10% Pd/C, 10w/w). The vessel was placed on a hydrogenation apparatus at 60 psig for 2-4 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide **262** (0.32 g, 95%) as brown oil. ^1H NMR

(400 MHz, DMSO- d_6) δ 6.92 (s, 1H), 6.85 (s, 1H), 6.53 (m, 1H), 6.49 (m, 1H), 4.51 (bs, 2H), 3.90 (t, J = 6 Hz, 2H), 3.09 (m, 2H), 2.08 (m, 2H), 1.99 (s, 3H), 1.22 (m, 9H).

Step E:

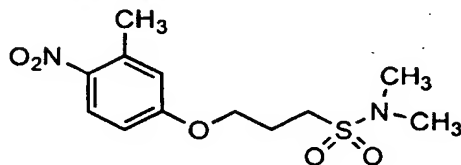
5 Acid 49 (120 mg, 0.37 mmol), oxalyl chloride (0.035 mL, 50 mg, 0.40 mmol), *N,N*-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline 262 (111 mg, 0.37 mmol), NaHCO_3 (155 mg, 1.85 mmol), acetone (10 mL), and water (0.5 mL) were used
10 according to general procedure VI. The product purified by flash chromatography using 5% MeOH: CH_2Cl_2 to afford 258 (28 mg, 12%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.08 (s, 1H), 7.63 (dd, J = 4, 8 Hz, 1H), 7.54 (m, 1H), 7.47 (d, J = 4 Hz, 1H), 7.41 (m, 2H), 7.20 (d, J = 8 Hz, 1H), 7.12 (d, J = 8 Hz, 1H), 6.87 (s, 1H), 6.75 (m, 1H), 6.68 (dd, J = 4, 8 Hz, 1H), 4.70 (s, 2H), 4.02 (t, J = 8 Hz, 2H), 3.09 (t, J = 8 Hz, 2H), 2.05 (t, J = 8
15 Hz, 2H), 2.00 (s, 3H), 1.22 (s, 9H). MS (ES): 608 (M-H) $^-$.

Example 108



263

Step A:

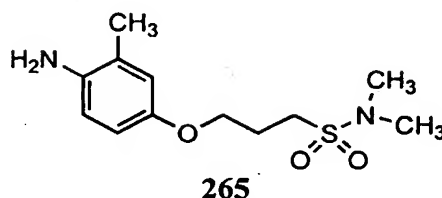


264

To a round-bottom flask equipped with a stir bar and a gas dispersion tube was added sulfonyl chloride 260 (3.8 g, 0.013 mol) and methylene chloride (100 mL), and the
25 reaction was cooled to 0 °C. Dimethylamine gas was bubbled through the reaction mixture for 1 h, after which time the reaction mixture was poured into CH_2Cl_2 and water. The organics were collected, washed with water, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to afford 264 (2.1 g, 54%) as a pale yellow

solid. The product was used in the next step without further purification or characterization.

Step B:



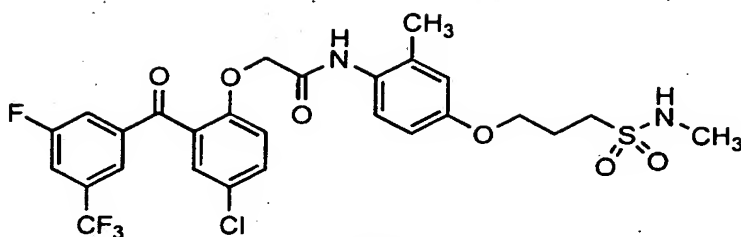
To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **264** (2.1 g, 7.0 mmol), absolute ethanol (40 mL), and palladium on charcoal (0.21 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 50 p.s.i. for 2-4 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide **265** (1.7 g, 90%) as a pale yellow solid. The product was used in the next step without further purification or characterization.

Step C:

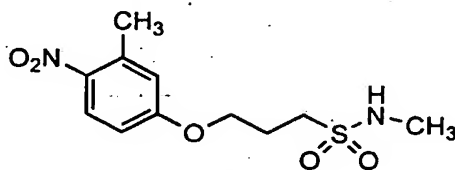
Acid **71** (120 mg, 0.32 mmol), oxalyl chloride (0.032 mL, 44 mg, 0.35 mmol), N,N-dimethylformamide (1 drop), and CH₂Cl₂ (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **265** (78 mg, 0.29 mmol), NaHCO₃ (134 mg, 1.6 mmol), acetone (6 mL), and water (0.5 mL) were used according to general procedure VI. The resulting residue was treated several times with pentane to afford **263** (90 mg, 45%) as a beige solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.09 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.84 (m, 2H), 7.65 (dd, J = 2.4, 8.8 Hz, 1H), 7.51 (d, J = 2.8 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 2.4 Hz, 1H), 6.68 (dd, J = 2.8, 8.8 Hz, 1H), 4.69 (s, 2H), 4.00 (t, J = 6 Hz, 2H), 3.13 (m, 2H), 2.75 (s, 6H), 2.05 (m, 2H), 1.98 (s, 3H). MS (ES): 631 (M⁺)

Example 109

195

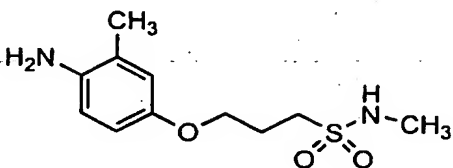


266

Step A:

267

To a round-bottom flask equipped with a stir bar and a gas dispersion tube was added sulfonyl chloride **260** (3.2 g, 0.011 mol) and methylene chloride (75 mL), and the reaction was cooled to 0 °C. Methylamine gas was bubbled through the reaction mixture for 1 h, after which time the reaction mixture was poured into CH₂Cl₂ and water. The organics were collected, washed with water, dried over MgSO₄, filtered and the solvents were removed under reduced pressure. The product was recrystallized from methanol to afford **267** (2.0 g, 63%) as a pale yellow solid. ¹H NMR (300 MHz, DMSO-d₆) δ 8.08 (d, J = 9 Hz, 1H), 7.03 (m, 3H), 4.23 (t, J = 8.4 Hz, 2H), 3.19 (m, 2H), 2.57 (m, 6H), 2.12 (m, 2H). MS (ES): 617 (M⁺).

Step B:

268

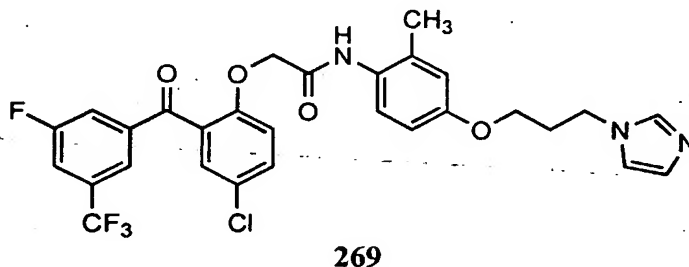
To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **267** (2.0 g, 6.9 mmol), toluene (25 mL), and palladium on charcoal (0.20 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 50 p.s.i. for 4 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure. The resulting residue was treated with several portions of hexanes to provide **268** (1.1 g, 62%) as a pink solid. ¹H NMR (400

MHz, DMSO- d_6) δ 6.92 (q, J = 5 Hz, 1H), 6.55 (s, 1H), 6.48 (m, 2H), 4.36 (bs, 2H), 3.88 (t, J = 6.4 Hz, 2H), 3.08 (m, 2H), 2.53 (d, J = 5 Hz, 3H), 1.95 (m, 5H).

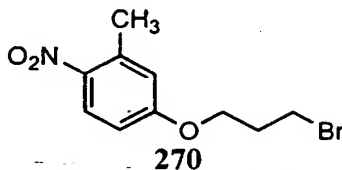
Step C:

- 5 Acid 71 (120 mg, 0.32 mmol), oxalyl chloride (0.032 mL, 44 mg, 0.35 mmol), *N,N*-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline 268 (75 mg, 0.29 mmol), NaHCO_3 (134 mg, 1.6 mmol), acetone (6 mL), and water (0.5 mL) were used according to general procedure VI. The resulting residue was treated several times with
- 10 hexanes to afford 266 (80 mg, 41%) as a beige solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.09 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.84 (m, 2H), 7.65 (dd, J = 2.4, 8.8 Hz, 1H), 7.52 (d, J = 2.8 Hz, 1H), 7.20 (d, J = 9.2 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.94 (q, J = 5 Hz, 1H), 6.74 (d, J = 2.8 Hz, 1H), 6.68 (dd, J = 2.8, 8.8 Hz, 1H), 4.68 (s, 3H), 4.00 (m, 2H), 3.10 (t, J = 8 Hz, 2H), 2.54 (d, J = 5 Hz), 2.01 (m, 5H). MS (ES): 617 (M^+).

15

Example 110**Step A:**

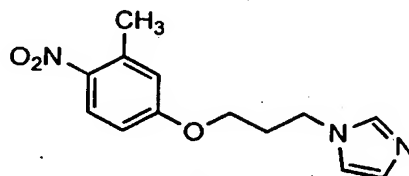
20



- Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-methyl-3-nitrophenol (5.0 g, 0.033 mol), dibromopropane (26 mL, 52.7 g, 0.26 mol),
- 25 potassium carbonate (6.8 g, 0.05 mol), and *N,N*-dimethylformamide (100 mL) and the mixture was allowed to stir at rt for 2.5 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, washed with water and brine, dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The resulting oil was distilled to afford 270

(8.0 g, 89%) a brown oil. ^1H NMR (400 MHz, DMSO- d_6) δ 8.01 (d, J = 9.2 Hz, 1H), 7.02 (d, J = 2.8 Hz, 1H), 6.96 (dd, J = 2.4, 8.8 Hz, 1H), 4.16 (t, J = 6 Hz, 2H), 3.63 (t, J = 6 Hz, 2H), 2.51 (s, 3H), 2.24 (m, 2H).

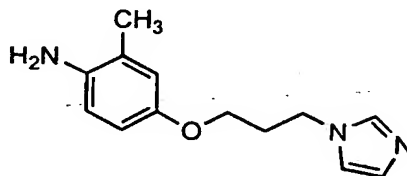
5 **Step B:**



271

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 270 (0.8 g, 2.9 mmol), imidazole (0.24 g, 3.49 mmol), potassium carbonate (0.8 g, 5.83 mmol), and N, N-dimethylformamide (20 mL) and the mixture was allowed to stir at 55 °C for 18 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography eluting with 1:1 hexanes:ethyl acetate to afford 271 (0.3 g, 40%). ^1H NMR (400 MHz, DMSO- d_6) δ 8.06 (d, J = 9 Hz, 1H), 7.65 (s, 1H), 7.22 (s, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.98 (dd, J = 2.7, 9 Hz, 1H), 6.92 (s, 1H), 4.16 (t, J = 7 Hz, 2H), 4.04 (t, J = 6 Hz, 2H), 2.57 (s, 3H), 2.22 (m, 2H).

Step C:



272

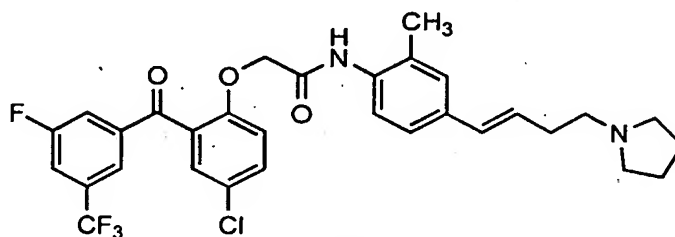
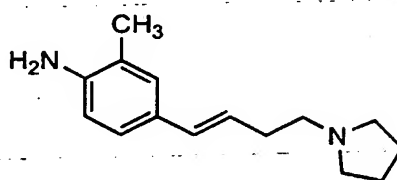
20

25

To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative 271 (0.3 g, 1.15 mmol), ethanol (20 mL), and palladium on-charcoal (30 mg of 10% Pd/C, 10% w/w). The vessel was placed on a hydrogenation apparatus at 55 p.s.i. for 2 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide 272 (0.23 g, 88%) a purple oil. ^1H NMR (400 MHz, DMSO- d_6) δ 7.57 (s, 1H), 7.14 (s, 1H), 6.85 (s, 1H), 6.54 (s, 1H), 6.48 (s, 2H), 4.44 (bs, 2H), 4.06 (t, J = 6.8 Hz, 2H), 3.70 (t, J = 6 Hz, 2H), 2.03 (m, 2H), 1.99 (s, 3H).

Step D:

Acid **71** (120 mg, 0.32 mmol), oxalyl chloride (0.032 mL, 44 mg, 0.35 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **272** (67 mg, 0.29 mmol), NaHCO_3 (134 mg, 1.6 mmol), acetone (6 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH: CHCl_3 as eluant to afford **269** (84 mg, 45%) as a pink solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.15 (s, 1H), 8.05 (d, $J = 9$ Hz, 1H), 7.90 (m, 2H), 7.71 (dd, $J = 3, 9$ Hz, 1H), 7.65 (s, 1H), 7.57 (d, $J = 3$ Hz, 1H), 7.24 (m, 2H), 7.13 (d, $J = 6$ Hz, 1H), 6.92 (s, 1H), 6.79 (d, $J = 3$ Hz, 1H), 6.73 (dd, $J = 3, 9$ Hz, 1H), 4.74 (s, 2H), 4.14 (t, $J = 6$ Hz, 2H), 3.88 (t, $J = 6$ Hz, 2H), 2.16 (m, 2H), 2.03 (s, 3H). MS (ES): 589 (M^+), 590 ($\text{M}+\text{H}$) $^+$.

Example 111**272****Step A:****273**

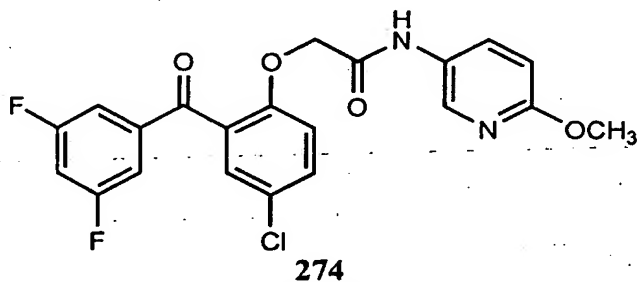
To a sealed-tube reaction vessel equipped with a stir bar and nitrogen on demand was added 4-bromo-2-methyl aniline (0.8 g, 4.3 mmol), palladium (II) acetate (97 mg, 0.43 mmol), tri-*o*-tolylphosphine (0.52 g, 1.72 mmol), N,N-dimethylformamide (15 mL), N-butylpyrrolidine (2.7 g, 21.5 mmol), and triethylamine (4.2 mL, 3.0 g, 30.1 mmol). The tube was sealed and allowed to stir at 80 °C for 18 h. When judged to be complete, the reaction was filtered through a pad of celite and the filtrate was poured into ethyl acetate and water. The organics were collected and washed with water and brine, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 93:7 CHCl_3 : MeOH as eluant to provide **273**.

(0.2 g, 20%) as a yellow oil. The product exists as a 2.7:1 mixture of E: Z isomers. ^1H NMR (400 MHz, DMSO- d_6) δ 6.87 (m, 2H), 6.51 (m, 1H), 6.18 (m, 1H), 5.87 (m, 1H), 4.81 (m, 2H), 2.44 (m, 8H), 2.31 (m, 2H), 2.00 (m, 2H), 1.85 (s, 3H). MS (ES): 231 (M+H) $^+$.

Step B:

Acid 71 (132 mg, 0.35 mmol), oxalyl chloride (0.034 mL, 48 mg, 0.38 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline 273 (72 mg, 0.31 mmol), NaHCO_3 (152 mg, 1.7 mmol), acetone (6 mL), and water (0.5 mL) were used according to general procedure VI. The product was recrystallized from absolute ethanol to afford 272 (20 mg, 10%) as a white solid. The product exists as a 2.7:1 mixture of E:Z isomers. ^1H NMR (400 MHz, DMSO- d_6) δ 9.15 (m, 1H), 7.98 (m, 1H), 7.85 (m, 2H), 7.65 (m, 1H), 7.51 (m, 1H), 7.20 (m, 4H), 6.32 (m, 1H), 6.21 (m, 1H), 4.72 (s, 2H), 2.46 (m, 8H), 2.31 (m, 2H), 2.04 (m, 2H), 1.65 (s, 3H). MS (ES): 590 (M+H) $^+$.

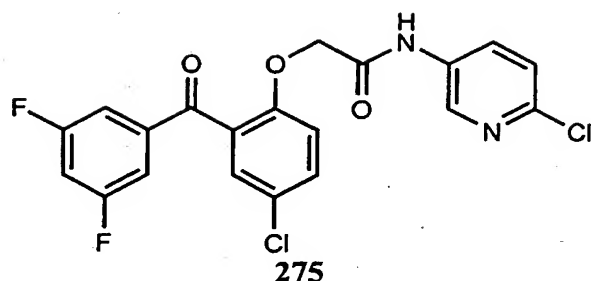
Example 112



The title compound was prepared according to General Procedure VI from acid 49 (0.51 mmol) and 5-amino-2-methoxypyridine (0.04 mL, 0.44 mmol). Purification by flash chromatography using 25% ethyl acetate/hexane as eluant, followed by trituration with ether gave 274 (0.146 g, 77%): mp 185-187 $^{\circ}\text{C}$; MS (ES+) m/z 433 (M+H); ^1H NMR (400 MHz, CDCl_3) δ 9.30 (s, 1 H), 8.49 (d, 1 H), 8.09 (dd, 1 H), 7.56 (dd, 1 H), 7.41-7.38 (m, 3 H), 7.13-7.09 (m, 1 H), 7.05 (d, 1 H), 6.76 (d, 1 H), 4.72 (s, 2 H), 3.94 (s, 3 H).

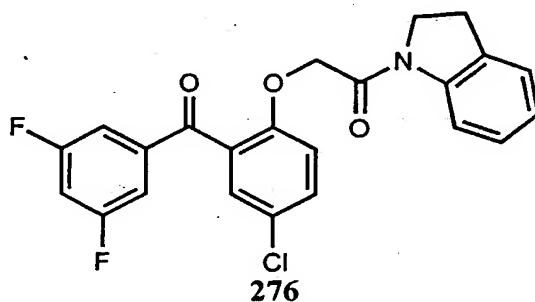
Example 113

200



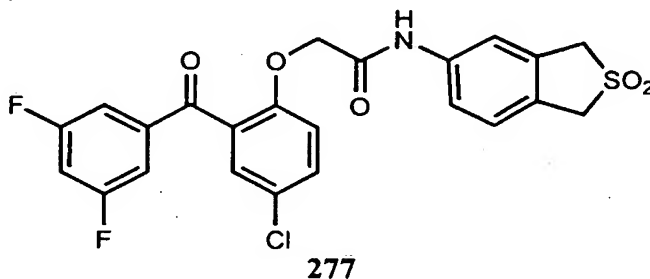
The title compound was prepared according to General Procedure VI from acid **49** (0.51 mmol) and 5-amino-2-methoxypyridine (0.05 mL, 0.44 mmol). Purification by flash chromatography using 25% ethyl acetate/hexane as eluant followed by trituration with ether gave **275** (0.134 g, 70%): mp 198-200 °C; MS (ES+) *m/z* 437 (M+H); ¹H NMR (400 MHz, CDCl₃) δ 9.79 (s, 1 H), 8.80 (d, 1 H), 8.30 (dd, 1 H), 7.58 (dd, 1 H), 7.41 (dd, 1 H), 7.39-7.38 (m, 2 H), 7.32 (d, 1 H), 7.15-7.11 (m, 1 H), 7.07 (d, 1 H), 4.76 (s, 2 H).

Example 114



The title compound was prepared according to General Procedure VI from acid **49** (0.51 mmol) and indoline (0.05 mL, 0.44 mmol). Purification by flash chromatography using 25% ethyl acetate/hexane as eluant followed by crystallization from methylene chloride/hexane gave **276** (0.069 g, 37%): mp 158-160 °C; MS (ES+) *m/z* 428 (M+H); ¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, 1 H), 7.44-7.39 (m, 4 H), 7.22-7.18 (m, 2 H), 7.07-6.97 (m, 3 H), 4.70 (s, 2 H), 3.98 (t, 2 H), 3.18 (t, 2 H) ppm.

Example 115

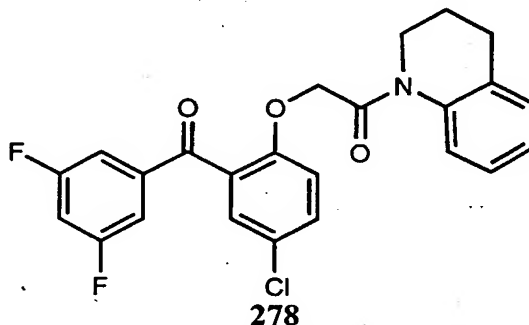


The title compound was prepared according to General Procedure VI from acid **49** (0.51 mmol) and 5-amino-1,3-dihydro-benzo[c]thiophene-2,2-dioxide (0.081 g, 0.44 mmol).

Purification by flash chromatography using 40-60% ethyl acetate/hexane as eluant followed by crystallization from ethyl acetate gave **277** (0.080 g, 37%): mp 197-199 °C;

5 MS (ES-) m/z 490 (M-H); ^1H NMR (400 MHz, CDCl_3) δ 9.43 (s, 1 H), 7.92 (s, 1 H), 7.65 (dd, 1 H), 7.57 (dd, 1 H), 7.41-7.38 (m, 3 H), 7.30 (d, 1 H), 7.15-7.10 (m, 1 H), 7.05 (d, 1 H), 4.72 (s, 2 H), 4.39 (s, 2 H), 4.35 (s, 2 H).

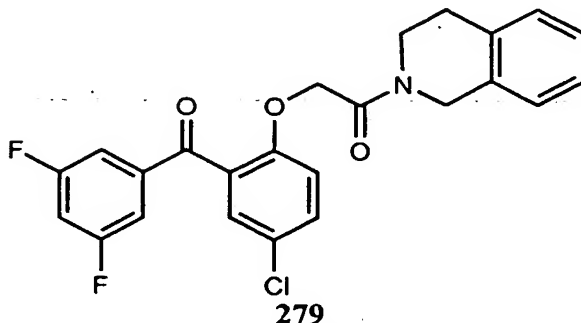
Example 116



10 The title compound was prepared according to General Procedure VI from acid **49** (0.49 mmol) and 1,2,3,4-tetrahydroquinoline (0.05 mL, 0.41 mmol). Isolation by flash chromatography using 15% ethyl acetate/hexane as eluant followed by trituration with hexanes gave **278** (0.081 g, 45%) in ca. 80% purity: MS (ES+) m/z 442 (M+H), 464

15 (M+Na); ^1H NMR (400 MHz, CDCl_3) δ 7.38 (dd, 1 H), 7.33-7.31 (m, 3 H), 7.11-7.09 (m, 3 H), 7.00-6.95 (m, 1 H), 6.88 (br s, 1 H), 4.73 (s, 2 H), 3.73 (br s, 2 H), 2.64 (br s, 2 H), 1.93-1.86 (m, 2 H).

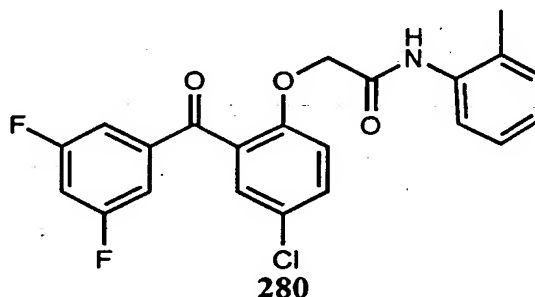
Example 117



20 The title compound was prepared according to General Procedure VI from acid **49** (0.49 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.035 mL, 0.41 mmol). Isolation by flash

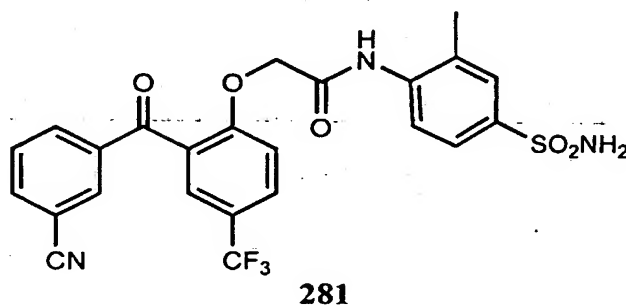
chromatography using 15% ethyl acetate/hexane as eluant followed by trituration with hexanes gave **279** (0.072 g, 40%) in ca. 80% purity: MS (ES+) m/z 442 (M+H), 464 (M+Na); ^1H NMR (400 MHz, CDCl_3) δ 7.43-7.39 (m, 1 H), 7.34-7.27 (m, 3 H), 7.19-7.15 (m, 2 H), 7.13-7.08 (m, 2 H), 7.02-6.93 (m, 2 H), 4.70 (s, 2 H), 4.65 (s, 1 H), 4.46 (s, 1 H), 3.73 (t, 1 H), 3.57 (t, 1 H), 2.81-2.75 (m, 2 H).

Example 118

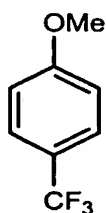


The title compound was prepared according to General Procedure VI from acid **49** (0.50 mmol) and *o*-toluidine (0.05 mL, 0.43 mmol). Isolation by flash chromatography using 10% ethyl acetate/hexane as eluant gave **280** (0.121 g, 58%): MS (ES+) m/z 416 (M+H), 438 (M+Na); MS (ES-) m/z 414 (M-H); ^1H NMR (400 MHz, CDCl_3) δ 8.30 (br s, 1 H), 7.71 (d, 1 H), 7.53 (dd, 1 H), 7.36 (d, 1 H), 7.34-7.31 (m, 2 H), 7.22-7.17 (m, 2 H), 7.09 (app t, 1 H), 7.05-7.01 (m, 2 H), 4.77 (s, 2 H), 2.18 (s, 3 H) ppm.

Example 119



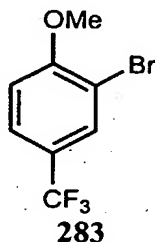
Step A:



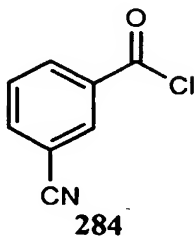
203

282

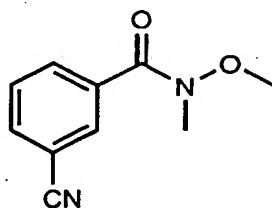
A mixture of trifluoro-*p*-cresol (18.9 g, 117 mmol), potassium carbonate (16.4 g, 119 mmol) and iodomethane (9.8 mL, 158 mmol) in 200 mL acetone was warmed to reflux for 8.5 h, then stirred at room temperature an additional 16 h. The reaction mixture was then concentrated *in vacuo*, and the residue was partitioned between 150 mL water and 150 mL ethyl acetate. The aqueous layer was extracted with another 150 mL of ethyl acetate, and the combined organic layers were then dried over MgSO₄, filtered and concentrated *in vacuo* to give **282** (18.97 g, 92%): ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, 2H), 6.96 (d, 2H), 3.85 (s, 3 H).

Step B:

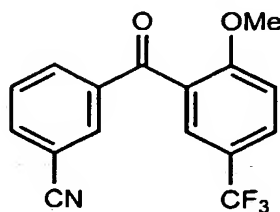
Bromine (4.1 mL, 79 mmol) was added dropwise to a solution of **282** (13.2 g, 75.2 mmol) and sodium acetate (6.48 g, 79 mmol) in 150 mL of glacial acetic acid over 35 min. The reaction mixture was stirred an additional 23 h at room temperature, then 10% NaHSO₃ (aq) was added until the orange reaction mixture became colorless. The mixture was then extracted with two 150-mL portions of CH₂Cl₂, and the combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo* to give 26.48 g of crude material. Purification by flash chromatography using 2% ethyl acetate/hexane as eluant gave **283** (2.232 g, 12%): ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, 1 H), 7.53 (dd, 1 H), 6.94 (d, 1 H), 3.93 (s, 3 H) ppm.

Step C:

Oxalyl chloride (48 mL, 96.5 mmol) was added dropwise over 1 h to a solution of 3-cyanobenzoic acid (5.767 g, 38.6 mmol) in 200 mL of CH₂Cl₂ and 0.10 mL of DMF, and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated *in vacuo* to give **284** (8.516 g), which was used immediately without further purification or characterization.

Step D:**285**

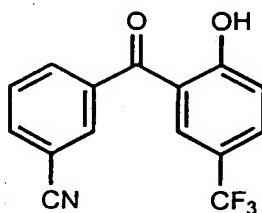
- 10 A solution of N,O-dimethylhydroxylamine (4.90 g, 50.2 mmol) in 20 mL of triethylamine and 100 mL of chloroform was cooled to 0 °C, and **284** (8.52 g, 38.6 mmol) was added dropwise over 10 min. The resulting mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature over 1.25 h. The reaction mixture was diluted with 150 mL ethyl acetate and washed with two 100-mL portions of water and a small portion of brine.
- 15 The organic layer was then dried over MgSO₄, filtered, and concentrated *in vacuo* to give **285** (6.381 g, 90%): ¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1 H), 7.95 (d, 1 H), 7.75 (d, 1 H), 7.55 (dd, 1 H), 3.54 (s, 3 H), 3.39 (s, 3 H).

Step E:**286**

- 20 *n*-Butyl lithium (7.7 mL of 1.6 M solution in hexanes) was added dropwise to a solution of **283** (2.735 g, 10.7 mmol) in 40 mL of ether at -78 °C over 15 min. The reaction mixture was stirred at -78 °C for an additional 15 min, then a solution of **285** (2.24 g, 11.8 mmol)
- 25 in 15 mL of ether was added dropwise over 20 min. The resulting mixture was stirred for

1 h at -78°C , then allowed to warm to room temperature and continue stirring for 4.67 h. The reaction mixture was quenched with the slow addition of 20 mL of water, stirred open to air for 45 minutes, and partitioned between 100 mL of ether and 100 mL of water. The organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo* to give 4.036 g of an orange liquid. Purification by flash chromatography using 5-10% ethyl acetate/hexane as eluant gave **286** (1.850 g, 57%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 8.01-7.99 (m, 2 H), 7.83 (d, 1 H), 7.78 (d, 1 H), 7.67 (s, 1 H), 7.59 (dd, 1 H), 7.08 (d, 1 H), 3.76 (s, 3 H).

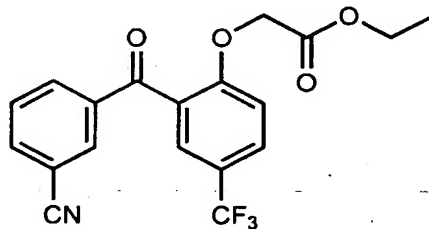
10 **Step F:**



287

The title compound (1.781 g, 100%) was prepared according to General Procedure IX from the anisole derivative **286** (1.805 g, 5.91 mmol). This intermediate was used without further purification: ^1H NMR (400 MHz, CDCl_3) δ 11.99 (s, 1 H), 7.97 (s, 1 H), 7.92 (d, 1 H), 7.87 (d, 1 H), 7.77 (dd, 1 H), 7.73 (s, 1 H), 7.69 (t, 1 H), 7.21 (d, 1 H).

Step G:



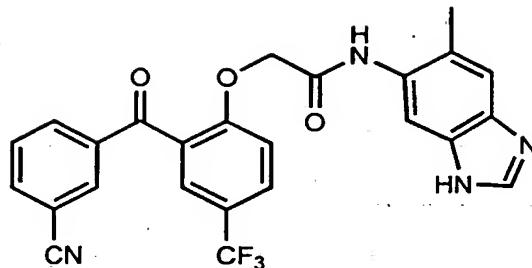
288

The title compound (2.196 g, 100%) was prepared according to General Procedure II from the phenol derivative **287** (1.78 g, 5.91 mmol). This intermediate was used without further purification: ^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1 H), 8.09 (d, 1 H), 7.82 (d, 1 H), 7.74

Compound **281** was prepared according to the General Procedure VI from the acid chloride **290** (0.49 mmol) and the aniline derivative **466** (0.076 g, 0.41 mmol). Purification by flash chromatography using 1% methanol/methylene chloride as eluant gave **281** (0.113 g, 53%): MS (ES+) m/z 516 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ 9.48 (s, 1 H), 8.20 (s, 1 H), 8.10-8.06 (m, 2 H), 7.94 (dd, 1 H), 7.80 (d, 1 H), 7.70 (app t, 1

H), 7.65-7.62 (m, 2 H), 7.57 (dd, 1 H), 7.36 (d, 1 H), 7.24 (s, 2 H), 4.90 (s, 2 H), 2.17 (s, 3 H).

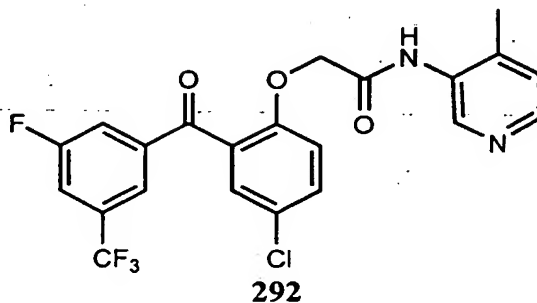
Example 120



291

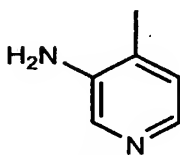
Compound 291 was prepared according to General Procedure VI from the acid chloride 290 (0.49 mmol) and the aniline derivative 210 (0.060 g, 0.41 mmol). Purification by flash chromatography using 1-3% methanol/methylene chloride, followed by crystallization from methylene chloride/hexane gave 291 (0.046 g, 20%): MS (ES+) m/z 479 (M+H); MS (ES-) m/z 477 (M-H); ^1H NMR (400 MHz, CD_3OD) δ 8.18–8.16 (m, 2 H), 8.07 (d, 1 H), 7.94–7.89 (m, 2 H), 7.79 (d, 1 H), 7.65 (app t, 1 H), 7.62 (s, 1 H), 7.44–7.41 (m, 2 H), 4.85 (s, 2 H), 2.20 (s, 3 H).

Example 121



292

Step A:



293

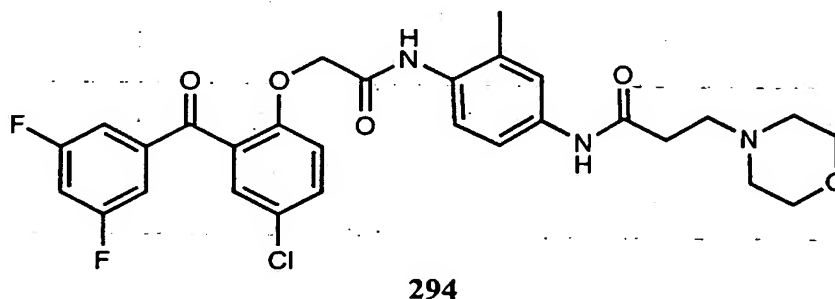
A mixture of 4-methyl-3-nitropyridine (1.102 g, 7.24 mmol) and 10% palladium on carbon (0.096 g) in 20 mL of methanol was stirred at room temperature under an atmosphere of 49 psi hydrogen gas for 2 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **293** (0.849 g, quant.): ^1H NMR (400 MHz, CDCl_3) δ 8.00 (s, 1 H), 7.92 (d, 1 H), 6.93 (d, 1 H), 3.59 (br s, 2 H), 2.14 (s, 3 H).

Step B:

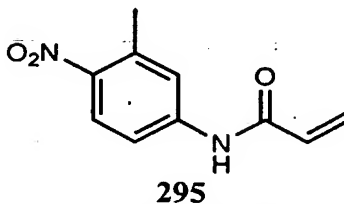
Compound **292** was prepared according to the General Procedure IV from the acid **71** (0.188 g, 0.5 mmol) and the aminopyridyl derivative **293** (0.065 g, 0.6 mmol).

Purification by flash chromatography using 0.5-2% methanol/methylene chloride as eluant gave **292** (0.071 g, 30%) as a white solid: MS (ES+) m/z 467 (M+H); MS (ES-) m/z 465 (M-H); ^1H NMR (400 MHz, CDCl_3) δ 8.84 (s, 1 H), 8.65 (s, 1 H), 8.35 (d, 1 H), 7.88 (s, 1 H), 7.70 (d, 1 H), 7.62-7.58 (m, 2 H), 7.40 (d, 1 H), 7.16 (d, 1 H), 7.10 (d, 1 H), 4.76 (s, 2 H), 2.26 (s, 3 H) ppm.

Example 122



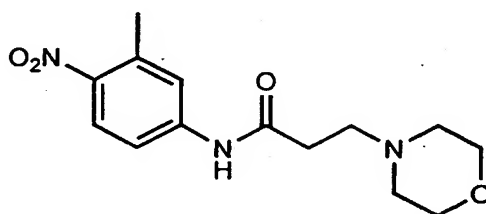
Step A:



A mixture of 3-methyl-4-nitroaniline (1.052 g, 6.91 mmol) and triethylamine (1.16 mL, 8.29 mmol) in 20 mL of methylene chloride was cooled to 0 °C and acryloyl chloride (0.62 mL, 7.61 mmol) was added dropwise over 5 min. The resulting mixture was stirred

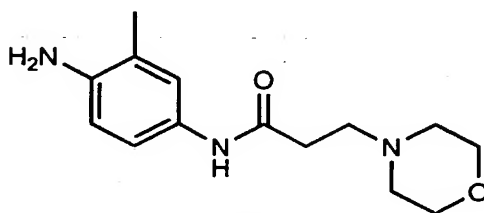
an additional 1.5 h at 0 °C, then diluted with 35 mL of methylene chloride, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to give **295** (1.941 g) which was used without further purification: ¹H NMR (400 MHz, CDCl₃) δ 8.52 (br s, 1 H), 8.01 (d, 1 H), 7.75 (d, 1 H), 7.65 (dd, 1 H), 6.49-6.40 (m, 2 H), 5.78 (dd, 1 H), 2.60 (s, 3 H).

5

Step B:**296**

A mixture of compound **295** (6.91 mmol) and morpholine (0.63 mL, 7.26 mmol) in 25 mL of ethanol was warmed to reflux for 2.3 h. The reaction mixture was then concentrated *in vacuo*, suspended in ethyl acetate, and filtered. The filtrate was concentrated *in vacuo*, dissolved in ethyl acetate, and allowed to crystallize. The crystalline impurity was removed by filtration, and the filtrate was concentrated *in vacuo* to give **296** (1.767 g, 87%): ¹H NMR (400 MHz, CDCl₃) δ 11.24 (br s, 1 H), 8.03 (d, 1 H), 7.54 (d, 1 H), 7.43 (dd, 1 H), 3.84-3.82 (m, 4 H), 2.76-2.73 (m, 2 H), 2.64 (br s, 4 H), 2.62 (s, 3 H), 2.58-2.55 (m, 2 H) ppm.

15

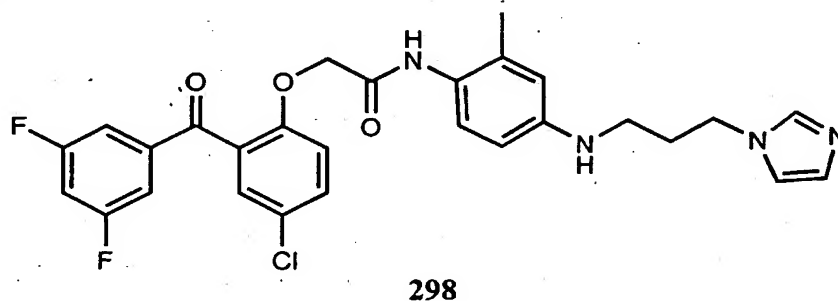
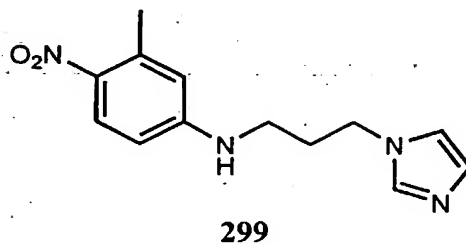
Step C:**297**

A mixture of compound **296** (0.202 g, 0.69 mmol) and 10% palladium on carbon (0.018 g) in 10 mL of methanol was stirred at room temperature under an atmosphere of 53 psi hydrogen gas for 2.17 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **297** (0.192 g, quant.): ¹H NMR (400 MHz, CDCl₃) δ 10.44 (br s, 1 H), 7.38 (s, 1 H), 7.27 (dd, 1 H), 6.76 (s, 1 H), 3.97-3.92 (m, 4 H), 2.91-2.83 (m, 2 H), 2.77-2.72 (m, 4 H), 2.66-2.62 (m, 2 H), 2.25 (s, 3 H).

25

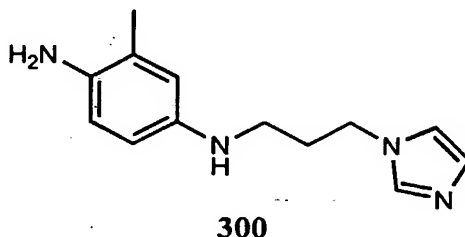
Step D:

Compound **294** was prepared according to the General Procedure VI from the acid chloride **49** (0.5 mmol) and the aniline derivative **297** (0.180 g, 0.68 mmol). Purification by flash chromatography using 1-2% methanol/methylene chloride as eluant gave **294** (0.203 g, 71%): MS (ES-) m/z 570 (M-H); ^1H NMR (400 MHz, CDCl_3) δ 10.64 (s, 1 H), 8.27 (s, 1 H), 7.57 (d, 1 H), 7.52-7.48 (m, 2 H), 7.35 (d, 1 H), 7.31-7.30 (m, 2 H), 7.22-7.20 (d, 1 H), 7.04-7.00 (m, 2 H), 4.64 (s, 2 H), 3.77 (br s, 4 H), 2.71-2.68 (m, 2 H), 2.57 (br s, 4 H), 2.50-2.47 (m, 2 H), 2.14 (s, 3 H).

Example 123**Step A:**

A mixture of 5-fluoro-2-nitrotoluene (0.24 mL, 2.0 mmol), 1-(3-aminopropyl)-imidazole (0.41 mL, 3.4 mmol), and sodium bicarbonate (0.302 g, 3.6 mmol) in 5 mL of pyridine and 0.5 mL of water was heated to reflux for 3 h. The reaction mixture was then partitioned between 50 mL of water and 50 mL of ethyl acetate. The organic layer was concentrated to give a yellow solid, which was purified by crystallization from ethyl acetate/hexane to provide **299** (0.255 g, 49%): ^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, 1

H), 7.60 (s, 1 H), 7.16 (s, 1 H), 7.08 (t, 1 H), 6.87 (s, 1 H), 6.47 (dd, 1 H), 6.40 (d, 1 H), 4.04-3.98 (m, 2 H), 3.06-3.01 (m, 2 H), 2.47 (s, 3 H), 1.98-1.91 (m, 2 H).

Step B:

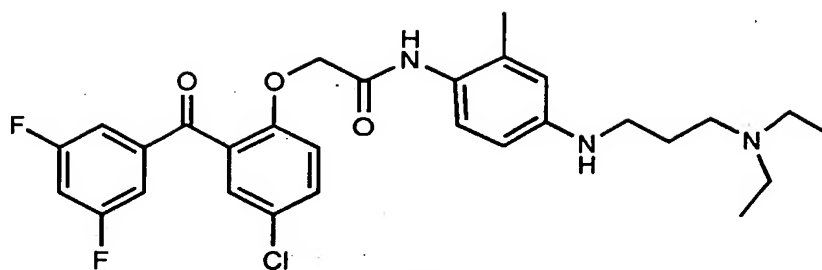
A mixture of compound 299 (0.233 g, 0.90 mmol) and 10% palladium on carbon (0.020 g) in 20 mL of methanol was stirred at room temperature under an atmosphere of 53 psi hydrogen gas for 1 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give 300 (0.166 g, 80%): ¹H NMR (400 MHz, CDCl₃) δ 7.48 (s, 1 H), 7.07 (s, 1 H), 6.92 (s, 1 H), 6.58 (d, 1 H), 6.40 (d, 1 H), 6.36 (dd, 1 H), 4.08 (t, 2 H), 3.49-3.48 (m, 1 H), 3.26 (br s, 2 H), 3.08-3.05 (m, 2 H), 2.13 (s, 3 H), 2.08-2.02 (m, 2 H).

Step C:

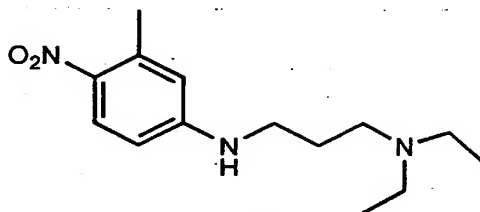
Compound 298 was prepared according to the General Procedure IV from the acid 49 (0.196 g, 0.6 mmol) and the aniline derivative 300 (0.155 g, 0.67 mmol). Purification by flash chromatography using 2% methanol/methylene chloride as eluant gave 298 (0.219 g, 68%): MS (ES+) *m/z* 539 (M+H); MS (ES-) *m/z* 537 (M-H); ¹H NMR (400 MHz, CDCl₃) δ 8.08 (s, 1 H), 7.55 (dd, 1 H), 7.49 (s, 1 H), 7.39 (d, 1 H), 7.35-7.31 (m, 2 H), 7.30 (d, 1 H), 7.08 (s, 1 H), 7.06-7.01 (m, 2 H), 6.93 (s, 1 H), 6.43-6.40 (m, 2 H), 4.67 (s, 2 H), 4.09-4.06 (m, 2 H), 3.54 (br s, 1 H), 3.11 (t, 2 H), 2.11-2.06 (m, 5 H).

Example 124

212

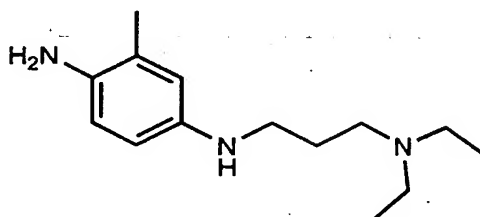


301

Step A:

302

A mixture of 5-fluoro-2-nitrotoluene (0.37 mL, 3.0 mmol), N,N-diethyl-1,3-propanediamine (0.80 mL, 5.1 mmol), and sodium bicarbonate (0.454 g, 5.4 mmol) in 7.5 mL of pyridine and 0.75 mL of water was heated to reflux for 3 h. The reaction mixture was stirred at room temperature an additional 3 h, then partitioned between 50 mL of water and 50 mL of ethyl acetate. The aqueous layer was extracted with an additional 20 mL of ethyl acetate, and the combined organic layers were then dried over MgSO₄, filtered, and concentrated *in vacuo* to give 0.833 g of crude material. Purification by flash chromatography using 1-5% methanol/methylene chloride as eluant gave **302** (0.742 g, 93%): ¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, 1 H), 6.66 (br s, 1 H), 6.34 (dd, 1 H), 6.27 (d, 1 H), 3.29-3.25 (m, 2 H), 2.61 (s, 3 H), 2.60-2.51 (m, 6 H), 1.81-1.75 (m, 2 H), 1.06 (t, 6 H).

Step B:

303

A mixture of compound **302** (0.730 g, 2.75 mmol) and 10% palladium on carbon (0.070 g) in 20 mL of methanol was stirred at room temperature under an atmosphere of 55 psi

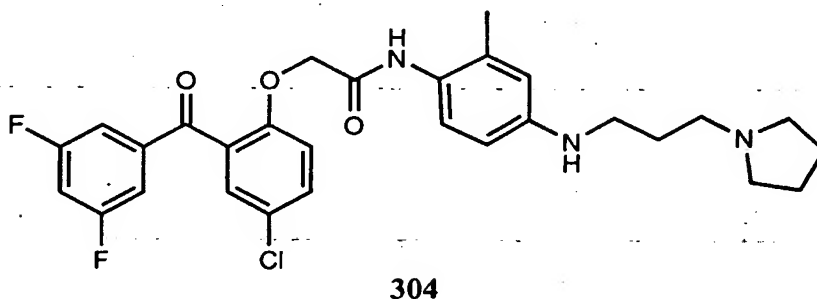
hydrogen gas for 1.17 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **303** (0.581 g, 90%): ^1H NMR (400 MHz, CDCl_3) δ 6.57 (d, 1 H), 6.42-6.37 (m, 2 H), 3.11-3.08 (m, 2 H), 2.54-2.49 (m, 6 H), 2.14 (s, 3 H), 1.78-1.71 (m, 2 H), 1.03 (t, 6 H).

5

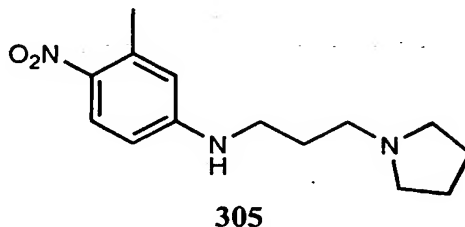
Step C:

Compound **301** was prepared according to the General Procedure IV from the acid **49** (0.196 g, 0.6 mmol) and the aniline derivative **303** (0.158 g, 0.67 mmol). Purification by flash chromatography using 3% methanol/0.1% triethylamine/methylene chloride as eluant, followed by crystallization from ethyl acetate/hexane gave **301** (0.113 g, 35%): MS (ES+) m/z 544 (M+H); MS (ES-) m/z 542 (M-H); ^1H NMR (400 MHz, CDCl_3) δ 7.96 (br s, 1 H), 7.54 (dd, 1 H), 7.39 (d, 1 H), 7.34-7.31 (m, 2 H), 7.25 (d, 1 H), 7.05-6.99 (m, 2 H), 6.43-6.41 (m, 2 H), 4.65 (s, 2 H), 3.15 (t, 2 H), 2.57-2.52 (m, 6 H), 2.07 (s, 3 H), 1.80-1.73 (m, 2 H), 1.05 (t, 6 H).

15

Example 125

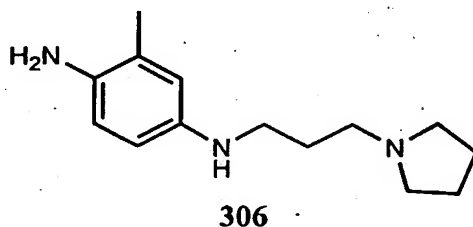
20

Step A:

A mixture of 5-fluoro-2-nitrotoluene (0.37 mL, 3.0 mmol), 1-(3-aminopropyl)pyrrolidine (0.64 mL, 5.1 mmol), and sodium bicarbonate (0.454 g, 5.4 mmol) in 7.5 mL of pyridine and 0.75 mL of water was heated to reflux for 3 h. The reaction mixture was stirred at

25

room temperature an additional 3 h, then partitioned between 50 mL of water and 50 mL of ethyl acetate. The aqueous layer was extracted with an additional 20 mL of ethyl acetate, and the combined organic layers were then dried over MgSO_4 , filtered, and concentrated *in vacuo* to give 0.758 g of crude material. Purification by flash chromatography using 0.5-10% methanol/methylene chloride as eluant gave **305** (0.595 g, 75%): ^1H NMR (400 MHz, CDCl_3) δ 8.06 (d, 1 H), 6.35 (dd, 1 H), 6.29 (d, 1 H), 6.09 (br s, 1 H), 3.30-3.26 (m, 2 H), 2.65-2.62 (m, 2 H), 2.61 (s, 3 H), 2.58-2.52 (m, 4 H), 1.86-1.78 (m, 6 H).

Step B:

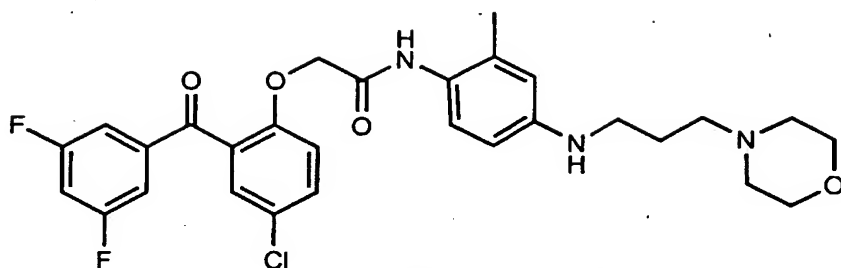
A mixture of compound **305** (0.590 g, 2.24 mmol) and 10% palladium on carbon (0.060 g) in 20 mL of methanol was stirred at room temperature under an atmosphere of 60 psi hydrogen gas for 1.33 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **306** (0.520 g, 99%): ^1H NMR (400 MHz, CDCl_3) δ 6.57 (d, 1 H), 6.42 (d, 1 H), 6.39 (dd, 1 H), 3.23 (br s, 2 H), 3.12 (t, 2 H), 2.56 (t, 2 H), 2.53-2.48 (m, 4 H), 2.13 (s, 3 H), 1.84-1.75 (m, 6 H) ppm.

Step C:

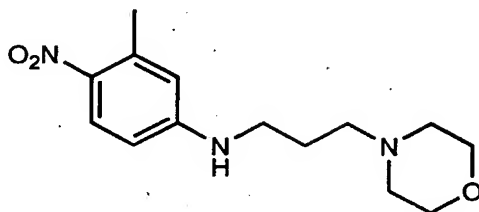
Compound **304** was prepared according to the General Procedure IV from the acid **49** (0.196 g, 0.6 mmol) and the aniline derivative **306** (0.156 g, 0.67 mmol). Purification by flash chromatography using 3% methanol/0.1% triethylamine/methylene chloride as eluant, followed by crystallization from ethyl acetate/hexane gave **304** (0.064 g, 20%): MS (ES+) m/z 542 (M+H); ^1H NMR (400 MHz, CDCl_3) δ 7.98 (s, 1 H), 7.54 (dd, 1 H), 7.39 (d, 1 H), 7.36-7.31 (m, 2 H), 7.26 (s, 1 H), 7.05-7.00 (m, 2 H), 6.44-6.42 (m, 2 H), 4.65 (s, 2 H), 3.18 (t, 2 H), 2.65-2.59 (m, 6 H), 2.07 (s, 3 H), 1.87-1.79 (m, 6 H).

Example 126

215

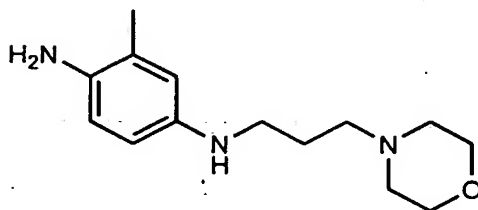


307

Step A:

308

A mixture of 5-fluoro-2-nitrotoluene (0.24 mL, 2.0 mmol), 4-(3-aminopropyl)morpholine (0.50 mL, 3.4 mmol), and sodium bicarbonate (0.302 g, 3.6 mmol) in 5 mL of pyridine and 0.5 mL of water was heated to reflux for 1 h. The reaction mixture was then partitioned between 50 mL of water and 50 mL of ethyl acetate, and the organic layer was dried over MgSO_4 , filtered, and concentrated *in vacuo* to give 0.493 g of crude material. Purification by flash chromatography using 1% methanol/methylene chloride as eluant gave **308** (0.279 g, 50%): ^1H NMR (400 MHz, CDCl_3) δ 8.06 (d, 1 H), 6.38 (dd, 1 H), 6.31 (s, 1 H), 5.92 (br s, 1 H), 3.77-3.75 (m, 4 H), 3.31-3.27 (m, 2 H), 2.6 (s, 3 H), 2.54-2.50 (m, 6 H), 1.85-1.79 (m, 2 H).

Step B:

309

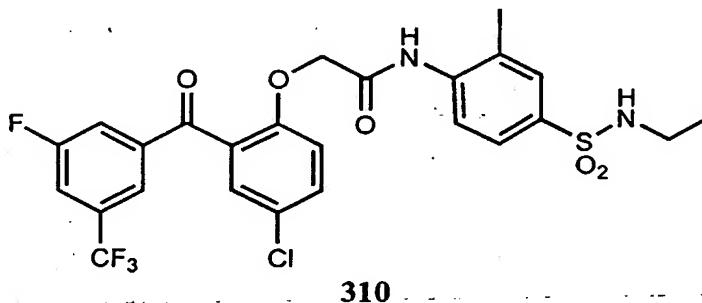
A mixture of compound **308** (0.266 g, 0.95 mmol) and 10% palladium on carbon (0.020 g) in 5 mL of methanol was stirred at room temperature under an atmosphere of 60 psi hydrogen gas for 2 h. The reaction mixture was then filtered through Celite and

concentrated *in vacuo* to give **309** (0.229 g, 97%): ^1H NMR (400 MHz, CDCl_3) δ 6.58 (d, 1 H), 6.43 (d, 1 H), 6.39 (dd, 1 H), 3.74-3.72 (m, 4 H), 3.14-3.11 (m, 2 H), 2.48-2.45 (m, 6 H), 2.14 (s, 3 H), 1.81-1.75 (m, 2 H).

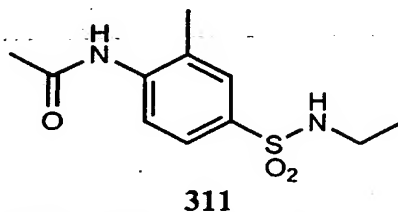
5 **Step C:**

Compound **307** was prepared according to the General Procedure IV from the acid **49** (0.092 g, 0.28 mmol) and the aniline derivative **309** (0.070 g, 0.28 mmol). Purification by flash chromatography using 3% methanol/0.1% triethylamine/methylene chloride as eluant gave **307** (0.101 g, 65%): MS (ES+) m/z 558 (M+H); ^1H NMR (400 MHz, CDCl_3) δ 8.00 (s, 1 H), 7.54 (dd, 1 H), 7.40-6.72 (m, 6 H), 6.62 (d, 1 H), 6.45-6.42 (m, 2 H), 4.66 (s, 2 H), 3.75-3.61 (m, 4 H), 3.17 (t, 2 H), 2.49-2.25 (m, 6 H), 2.08 (s, 3 H), 1.82-1.51 (m, 2 H).

Example 127



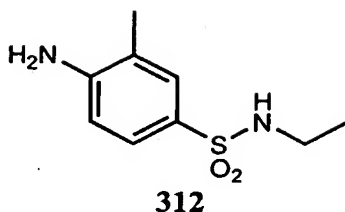
Step A:



20 A mixture of sulfonyl chloride **464** (1.10 g, 4.4 mmol), ethylamine (3.3 mL of 2.0 M THF solution, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in 50 mL of methylene chloride was stirred at room temperature for 11 d. The reaction mixture was then diluted with 50 mL of water and filtered to give 0.605 g of crude material. Crystallization from methanol gave **311** (0.425 g, 38%): ^1H NMR (400 MHz, CDCl_3) δ 9.40 (s, 1 H), 7.73 (d, 1 H), 7.58 (d, 1 H), 7.53 (dd, 1 H), 7.39 (t, 1 H), 2.75-2.68 (m, 2 H), 2.26 (s, 3 H), 2.07 (s, 3 H), 0.93 (t, 3 H).

25

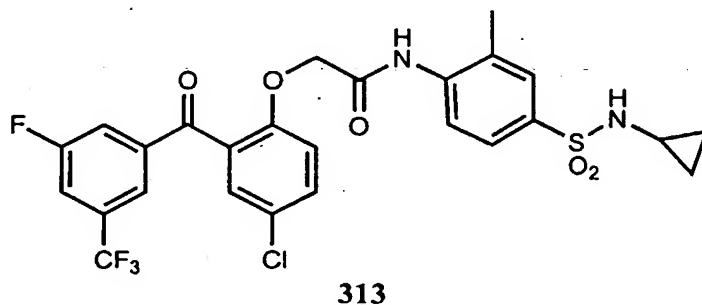
217

Step B:**312**

- 5 A mixture of compound 311 (0.308 g, 1.2 mmol), 1.5 M HCl (2.5 mL), and ethanol (12 mL) was heated to 80 °C for 18 h, then stirred at room temperature an additional 1 h. The reaction mixture was poured into 50 mL saturated NaHCO_3 (aq) and extracted with two 30-mL portions of methylene chloride. The combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo* to give 312 (0.337 g), which was used without
- 10 further purification: ^1H NMR (400 MHz, CDCl_3) δ 7.54 (m, 2 H), 6.68 (d, 1 H), 4.29 (t, 1 H), 4.07 (br s, 2 H), 3.00-2.93 (m, 2 H), 2.18 (s, 3 H), 1.10 (t, 3 H).

Step C:

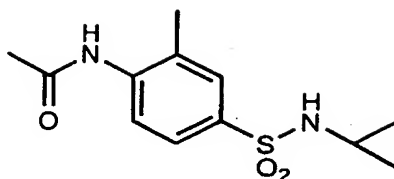
- 15 Compound 310 was prepared according to the General Procedure IV from the acid 71 (0.188 g, 0.5 mmol) and the aniline derivative 312 (0.169 g, 0.6 mmol). Purification by flash chromatography using 15-25% ethyl acetate/hexane as eluant gave 310 (0.016 g, 6%): MS (ES+) m/z 573 (M+H); MS (ES-) m/z 571 (M-H); ^1H NMR (400 MHz, CDCl_3) δ 8.67 (s, 1 H), 8.08 (d, 1 H), 7.88 (s, 1 H), 7.69 (m, 3 H), 7.59 (dd, 2 H), 7.38 (d, 1 H), 7.09
- 20 (d, 1 H), 4.74 (s, 2 H), 3.03-2.95 (m, 2 H), 2.31 (s, 3 H), 1.11 (t, 3 H).

Example 128**313**

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Step A:

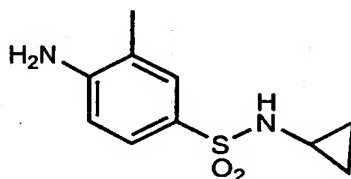
218



314

A mixture of sulfonyl chloride 464 (1.10 g, 4.4 mmol), cyclopropylamine (0.46 mL, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in 50 mL of methylene chloride was stirred at room temperature for 6 d. The reaction mixture was then filtered to give 0.800 g of crude material. Crystallization from methanol gave **314** (0.329 g, 28%): ^1H NMR (400 MHz, CDCl_3) δ 9.41 (s, 1 H), 7.78 (s, 1 H), 7.77-7.60 (m, 2 H), 7.56 (dd, 1 H), 2.27 (s, 3 H), 2.08 (s, 3 H), 2.06-2.03 (m, 1 H), 0.45-0.42 (m, 2 H), 0.36-0.34 (m, 2 H).

10 Step B:



315

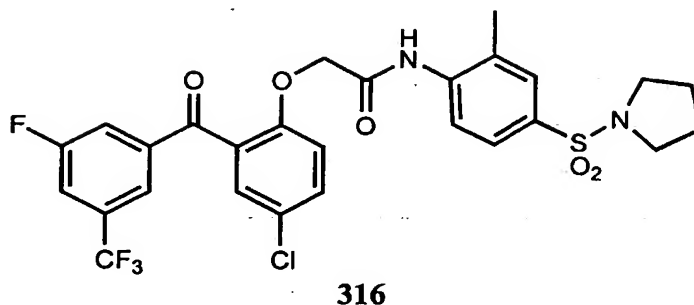
A mixture of compound **314** (0.324 g, 1.2 mmol), 1.5 M HCl (2.5 mL), and ethanol (12 mL) was heated to 80 °C for 18 h, then stirred at room temperature an additional 1 h. The reaction mixture was poured into 25 mL saturated NaHCO_3 (aq) and extracted with two 25-mL portions of methylene chloride. The combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo* to give **315** (0.256 g, 94%), which was used without further purification: ^1H NMR (400 MHz, CDCl_3) δ 7.57-7.55 (m, 2 H), 6.69 (d, 1 H), 4.81 (br s, 2 H), 2.22-2.19 (m, 4 H), 0.59-0.55 (m, 4 H).

20 Step C:

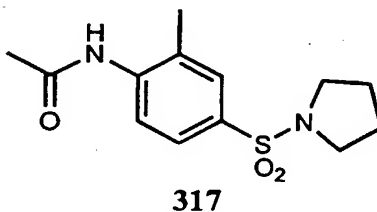
Compound **313** was prepared according to the General Procedure IV from the acid **71** (0.188 g, 0.5 mmol) and the aniline derivative **315** (0.124 g, 0.55 mmol). Purification by flash chromatography using 15-25% ethyl acetate/hexane as eluant gave **313** (0.026 g, 9%): MS (ES+) m/z 585 (M+H); MS (ES-) m/z 583 (M-H); ^1H NMR (400 MHz, CDCl_3) δ 8.68 (s, 1 H), 8.12 (d, 1 H), 7.88 (s, 1 H), 7.75-7.71 (m, 3 H), 7.59 (dd, 2 H), 7.47-7.43 (m,

1 H), 7.38 (d, 1 H), 7.08 (d, 1 H), 4.75 (s, 2 H), 2.32 (s, 3 H), 2.25-2.19 (m, 1 H), 0.63-0.57 (m, 4 H).

Example 129



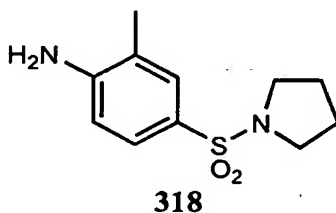
Step A:



A mixture of sulfonyl chloride 464 (1.10 g, 4.4 mmol), pyrrolidine (0.55 mL, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in 50 mL of methylene chloride was stirred at room temperature for 6 d. The reaction mixture was then filtered, and the filter cake was washed with methylene chloride and methanol and dried with a vacuum pump to give 317 (0.696 g, 56%): ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1 H), 7.82 (d, 1 H), 7.60 (d, 1 H), 7.55 (dd, 1 H), 3.10-3.07 (m, 4 H), 2.28 (s, 3 H), 2.09 (s, 3 H), 1.64-1.58 (m, 4 H).

15

Step B:

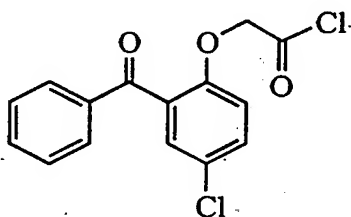


A mixture of compound 317 (0.690 g, 2.44 mmol), 1.5 M HCl (5.0 mL), and ethanol (25 mL) was heated to 80 °C for 18 h, then stirred at room temperature an additional 7 h. The reaction mixture was filtered to give 318 (0.369 g, 63%): ¹H NMR (400 MHz, CDCl₃) δ

7.29-7.26 (m, 2 H), 6.64 (d, 1 H), 5.73 (br s, 2 H), 3.01-2.98 (m, 4 h), 2.05 (s, 3 H), 1.60-1.56 (m, 4 H).

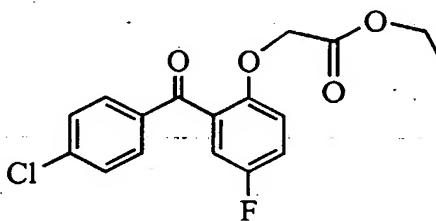
Step C:

- 5 Compound 316 was prepared according to the General Procedure IV from the acid 71 (0.188 g, 0.5 mmol) and the aniline derivative 318 (0.132 g, 0.55 mmol). Purification by flash chromatography using 15-25% ethyl acetate/hexane as eluant gave 316 (0.013 g, 4%): MS (ES+) m/z 599 (M+H); MS (ES-) m/z 597 (M-H); ^1H NMR (400 MHz, DMSO- d_6) δ 9.36 (s, 1 H), 7.97-7.01 (m, 9 H), 4.78 (s, 2 H), 3.08-3.04 (m, 4 H), 2.15 (s, 3 H),
10 1.59-1.56 (m, 4 H).



320

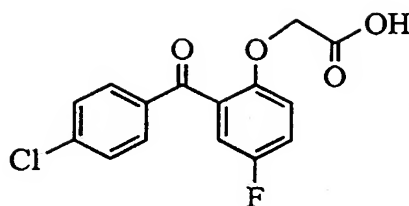
- Carboxylic acid 105 (5 g, 17 mmol), methylene chloride (90 mL), and thionyl chloride (13.2 mL, 18 mmol) were used as described in general procedure XV to afford 320 as an
15 orange oil (5.31 g). The crude product was used without further purification.



321

- 20 4'-Chloro-5-fluoro-2-hydroxybenzophenone (Lancaster, 5 g, 20 mmol), potassium carbonate (13.8 g, 100 mmol), ethyl bromoacetate (2.5 mL, 23 mmol), and acetone (200 mL) were used as in general procedure II to afford 321 as an orange/off-white solid (6.72 g, crude material). ^1H NMR (DMSO- d_6 , 300 MHz) δ 1.2 (t, 3H), 4.1 (m, 2H), 4.75 (s, 2H), 7.15 (dd, 1H), 7.3 (dd, 1H), 7.35-7.4 (m, 1H), 7.6 (d, 2H), 7.8 (d, 2H).

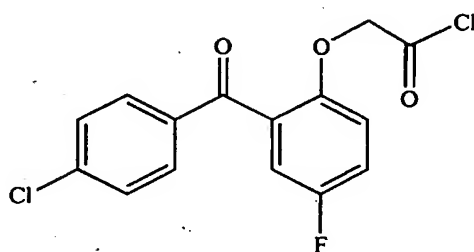
221



322

Ester **321** (6.72 g, 20 mmol), ethanol (80 mL), water (20 mL), and lithium hydroxide monohydrate (1 g, 24 mmol) were used as in general procedure III to afford carboxylic acid **322** as off-white solid (6.56 g, crude material). ¹H NMR (DMSO-d₆, 300 MHz) δ 4.7 (s, 2H), 7.1 (d, 1H), 7.3 (d, 1H), 7.4 (m, 1H), 7.6 (d, 2H), 7.8 (d, 2H), 13 (bs, 1H); MS (ES⁻) *m/z* 307 (M-H)⁻.

10



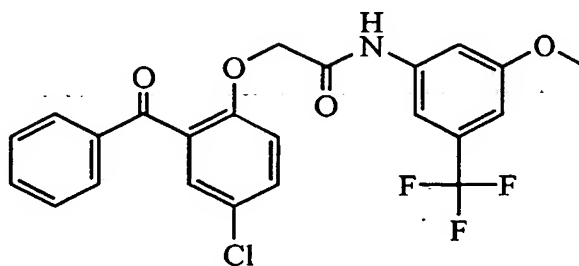
323

Into a round-bottom flask were placed acid **322** (3 g, 10 mmol) and thionyl chloride (51 mL of a 2N solution in methylene chloride, 102 mmol). After refluxing for 1 1/2 h, the mixture was concentrated in vacuo to give **323** as a dark purple oil, which was used without characterization or purification.

15

Example 130

20



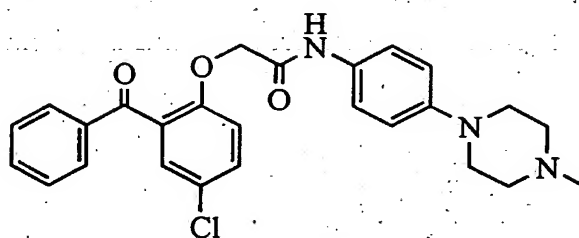
324

3-Methoxy-5-(trifluoromethyl)aniline (Aldrich, 0.309 g, 1.62 mmol), NEt₃ (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (7

25

mL) were used as in general procedure X. The product was purified by flash chromatography using a gradient between 9:1 and 4:1 hexanes:ethyl acetate to afford **324** as an off-white solid (0.17 g, 23%). ¹H NMR (DMSO-d₆, 300 MHz) δ 3.8 (s, 3H), 4.7 (s, 2H), 7 (s, 1H), 7.2 (d, 1H), 7.4 (s, 1H), 7.5 (m, 4H), 7.6 (m, 2H), 7.8 (d, 2H), 10 (s, 1H); MS (ES⁻) m/z 462 (M-H)⁻.

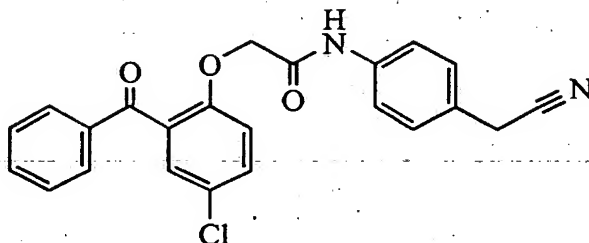
Example 131



325

4-(N-Methylpiperazinyl)aniline (Biomet Research Ltd., 0.237 g, 1.24 mmol), NEt₃ (0.26 mL, 1.87 mmol), acetonitrile (5 mL), and acid chloride **320** (0.38 g, 1.24 mmol) in acetonitrile (2 mL) were used as in general procedure X. The product was purified by flash chromatography using a gradient between 49:1 and 24:1 methylene chloride:methanol to afford **325** as a yellow solid (0.16 g, 27%). ¹H NMR (DMSO-d₆, 300 MHz) δ 2.2 (s, 3H), 2.4 (t, 4H), 3.1 (t, 4H), 4.7 (s, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.3 (d, 2H), 7.5 (s, 1H), 7.55 (t, 2H), 7.6-7.7 (m, 2H), 7.8 (d, 2H) 9.5 (s, 1H); MS (ES⁻) m/z 462 (M-H)⁻.

Example 132

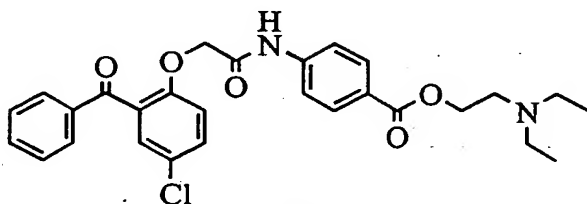


326

4-Aminophenyl acetonitrile (Aldrich, 0.214 g, 1.62 mmol), NEt₃ (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (7 mL) were used as in general procedure X. The product was purified by flash chromatography using

7:3 hexanes:ethyl acetate with 0.01% NEt₃ to afford **326** as an orange solid (0.26 g, 40%).
¹H NMR (DMSO-d₆, 300 MHz) δ 4 (s, 2H), 4.7 (s, 2H), 7.2 (d, 1H), 7.3 (d, 2H), 7.45 (s, 1H), 7.5-7.6 (m, 4H), 7.65 (m, 2H), 7.8 (d, 2H), 9.9 (s, 1H); MS (ES⁻) *m/z* 403 (M-H)⁻.

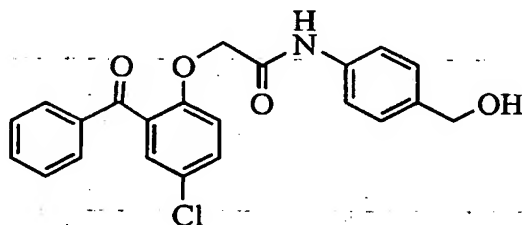
Example 133



327

Procaine (ICN, 0.382 g, 1.62 mmol), NEt₃ (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.38 g, 1.24 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using 24:1 methylene chloride:methanol to afford **327** as an off-white solid (0.037 g, 4.5%). ¹H NMR (DMSO-d₆, 300 MHz) δ 1 (t, 6H), 2.8 (bs, 2H), 4.3 (bs, 2H), 4.8 (bs, 2H), 7.2 (d, 1H), 7.5-7.7 (m, 8H), 7.8 (d, 2H), 7.9 (d, 2H), 10.2 (s, 1H); MS (AP⁺) *m/z* 509 (M+H)⁺.

Example 134

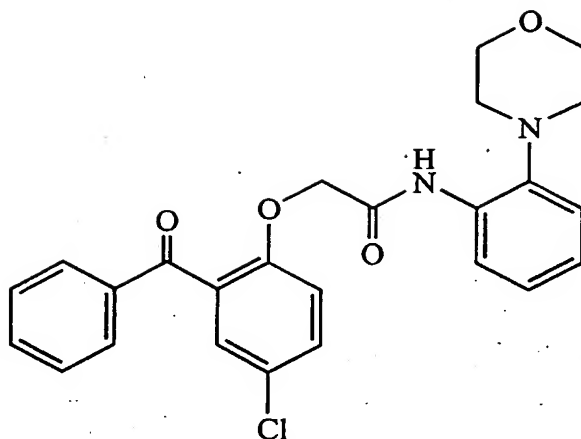


328

4-Amino benzyl alcohol (Fluka, 0.2 g, 1.62 mmol), NEt₃ (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using 4:1 hexanes:ethyl acetate to afford **328** as a dark yellow solid (0.06 g, 10%). ¹H NMR (DMSO-d₆, 300 MHz) δ 4.45 (d, 2H), 4.7 (s, 2H), 5.1 (t, 1H), 7.2 (t, 3H), 7.45 (t, 3H), 7.55 (t, 2H), 7.6 (t, 2H), 7.8 (d, 2H), 9.7 (s, 1H); MS (ES⁻) *m/z* 394 (M-H)⁻.

Example 135

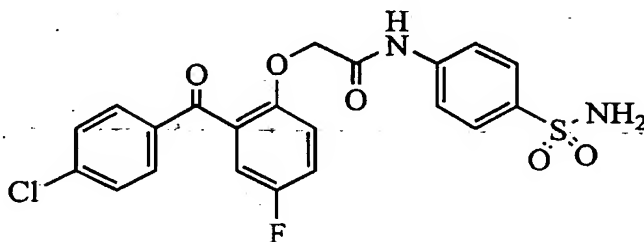
224



329

2-Morpholinoaniline (Lancaster, 0.288 g, 1.62 mmol), NEt_3 (0.23 mL, 1.65 mmol),
5 acetonitrile (5 mL), and acid chloride 320 (0.5 g, 1.62 mmol) in acetonitrile (5 mL) were
used as in general procedure X. The product was purified by flash chromatography using
a gradient between 9:1 and 4:1 hexanes:ethyl acetate to afford 329 as an off-white solid
(0.082 g, 11%). ^1H NMR (DMSO-d_6 , 400 MHz) δ 2.65 (s, 4H), 3.5 (s, 4H), 4.7 (s, 2H),
7.1 (t, 2H), 7.15 (s, 1H), 7.3 (d, 1H), 7.4 (t, 2H), 7.5 (m, 2H), 7.6 (d, 1H), 7.7 (d, 2H), 7.9
10 (s, 1H), 8.7 (s, 1H); MS (ES^+) m/z 451 ($\text{M}+\text{H}^+$).

Example 136



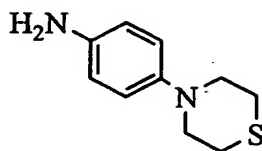
330

Sulfanilamide (Aldrich, 0.263 g, 1.53 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5
mL), and acid chloride 323 (0.5 g, 1.53 mmol) in acetonitrile (5 mL) were used as in
general procedure X. The reaction mixture was concentrated under reduced pressure,
20 triturated with methylene chloride, ethyl acetate, hexanes, and methanol, and filtered. The
resulting solid was washed with diethyl ether and ethyl acetate to give an off-white solid,
which was triturated with water and filtered to give 330 as an off-white solid (0.078 g,
11%). ^1H NMR (DMSO-d_6 , 400 MHz) δ 4.7 (s, 2H), 7.15 (dd, 1H), 7.2 (s, 2H), 7.25 (d,

4-Nitro-bromobenzene (Aldrich, 10.31 g, 51 mmol) in pyridine (85 mL), sodium bicarbonate (7.5 g, 89 mmol), and water (3 mL) were used as in general procedure XI to

afford 333 as a yellow crystalline solid (6.5g, 57%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.6 (t, 4H), 3.8 (t, 4H), 7 (d, 2H), 8 (d, 2H); MS (ES⁺) *m/z* 225 (M+H)⁺.

Step B:



334

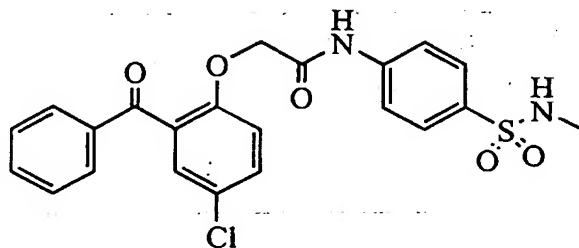
Compound 333 (1.04 g, 4.63 mmol), palladium on carbon (0.2 g, 10% w/w), ethanol (20 mL) and THF (20 mL) were used as in general procedure XII to afford 334 as a brown solid (0.95 g, crude material).

Step C:

Compound 334 (0.95 g, 4.9 mmol), NEt₃ (1 mL, 7.2 mmol), acetonitrile, and acid chloride 320 (1.51 g, 4.9 mmol) in acetonitrile (20 mL total reaction volume) were used as in general procedure X without heat. The reaction mixture was filtered and washed with acetonitrile followed by diethyl ether to afford 332 as an off-white solid (1.154g, 51%).

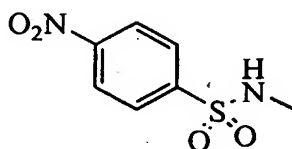
¹H NMR (DMSO-d₆, 400 MHz) δ 2.6 (m, 4H), 3.4 (m, 4H), 4.6 (s, 2H), 6.9 (d, 2H), 7.15 (d, 1H), 7.3 (d, 2H), 7.4 (s, 1H), 7.5 (t, 2H), 7.55-6.5 (m, 2H), 7.8 (d, 2H), 9.45 (s, 1H); MS (ES⁻) *m/z* 465 (M-H)⁻.

Example 139



335

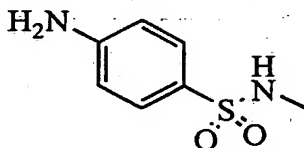
Step A:



227

336

4-Nitrobenzenesulfonylchloride (Aldrich, 44.3 g, 200 mmol) was added portionwise to a solution of methylamine in ethanol (250 mL, 208 mmol) which was stirred at 0 °C under nitrogen. After removing the ice bath, the reaction was stirred for 45 min. Water (250 mL) was added and the resulting product was filtered to afford **336** as a crystalline solid (37.6 g, 87%). The crude material was used without purification.

Step B:**337**

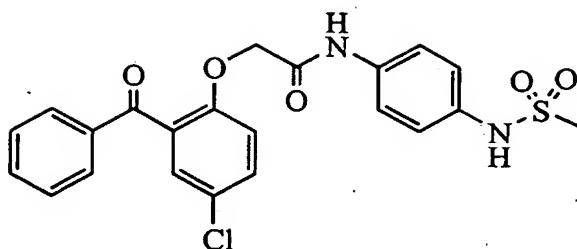
Palladium on carbon (2 g, 10% w/w) was added to a solution of compound **336** (17.3 g, 80 mmol), methanol (80 mL), THF (80 mL), and hydrochloric acid (concentrated, 7 mL, 84 mmol) and used as in general procedure XII to afford **337** as a white solid (14.3 g, 80%). The crude material was used without purification.

Step C:

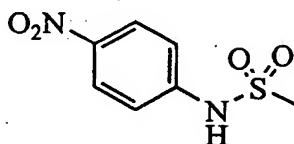
Compound **337** (0.32 g, 1.44 mmol), NEt_3 (0.5 mL, 3.6 mmol), acetonitrile (5 mL), and acid chloride **320** (0.444 g, 1.44 mmol) in acetonitrile (5 mL) were used as in general procedure X. After 6 d, another equivalent of acid chloride **320** (0.444 g, 1.44 mmol) was added and the solution was stirred. The reaction mixture was filtered and the resulting solid was washed with acetonitrile and water, and suspended in ethyl acetate. The suspension was filtered and the filtrate concentrated in vacuo to afford **335** as an off-white solid (0.152 g, 23%). ^1H NMR (DMSO-d_6 , 400 MHz) δ 2.3 (d, 3H), 4.7 (s, 2H), 7.15 (d, 1H), 7.3 (m, 1H), 7.45 (s, 1H), 7.5 (t, 2H), 7.54-7.62 (m, 2H), 7.7 (s, 4H), 7.8 (d, 2H), 10.2 (s, 1H); MS (ES^-) m/z 457 (M-H).

Example 140

228



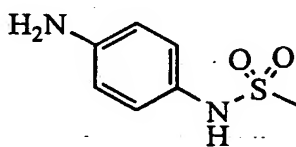
338

5 **Step A:**

339

Methanesulfonyl chloride (5 g, 43.9 mmol) was added dropwise to a solution of 4-nitroaniline (Aldrich, 5.95 g, 43.1 mmol) in dry pyridine (100 mL) which was stirred at –
10 15°C under nitrogen. After storing the resulting solution at 0°C for 2 d, the solvent was removed in vacuo. The product was triturated with ice water, filtered, and washed with ice water to afford **339** as an orange/yellow solid (8.87 g, 95%). The crude product was used without purification.

15

Step B:

340

Palladium on carbon (0.14 g, 10% w/w) was added to a solution of compound **339** (1.0 g, 4.63 mmol), ethanol (15 mL), and THF (20 mL) and the resulting suspension was used as
20 in general procedure XII with 50 psi of hydrogen to afford **340** as an orange oil (0.85 g). The crude material was used without purification.

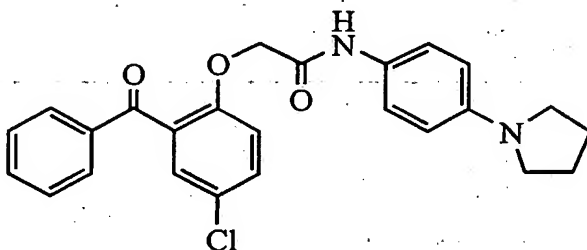
Step C:

25 Compound **340** (0.85 g, 4.6 mmol), NEt₃ (0.87 mL, 6.2 mmol), acetonitrile (8 mL), and acid chloride **320** (1.29 g, 4.2 mmol) in acetonitrile (8 mL) were used as in general procedure X. After 2 d, water was added and the resulting mixture was extracted with

ethyl acetate. The organic layer was separated, washed with water, dried over MgSO_4 , and concentrated in vacuo. The product was purified by flash chromatography using 35% ethyl acetate in hexanes to afford 338 as an off-white/ pale yellow solid (0.480 g, 23%).

^1H NMR (DMSO-d_6 , 300 MHz) δ 2.95 (s, 3H), 4.7 (s, 2H), 7.15 (d, 2H), 7.2 (d, 1H), 7.45 (d, 3H), 7.7 (m, 7H), 7.85 (d, 2H), 9.6 (s, 1H), 9.8 (s, 1H); MS (ES $^-$) m/z 457 (M-H).

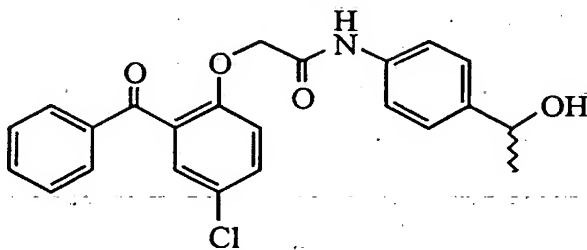
Example 141



341

4-(N-pyrrolidine)aniline (Apin, 0.262 g, 1.61 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride 320 (0.5 g, 1.62 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using a gradient between 9:1 and 4:1 hexanes:ethyl acetate to afford 341 as an off-white solid (0.112 g, 16%). ^1H NMR (DMSO-d_6 , 300 MHz) δ 2 (t, 4H), 3.2 (t, 4H), 4.66 (s, 2H), 6.5 (d, 2H), 7.2 (s, 1H), 7.3 (t, 2H), 7.45 (s, 1H), 7.5 (t, 2H), 7.6 (m, 2H), 7.8 (d, 2H), 9.3 (s, 1H); MS (ES $^-$) m/z 433 (M-H).

Example 142



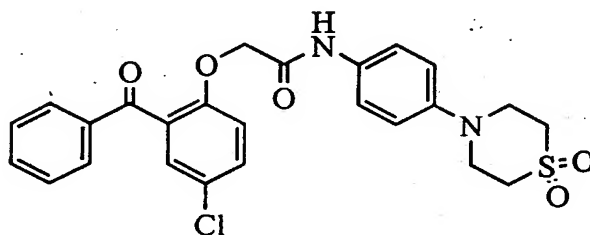
342

1-(4-Aminophenyl) ethanol (Apin, 0.25 g, 1.82 mmol), NEt_3 (0.25 mL, 1.79 mmol), acetonitrile (7 mL), and acid chloride 320 (0.51 g, 1.65 mmol) in acetonitrile (6 mL) were used as in general procedure X. The product was purified by flash chromatography using 45% ethyl acetate in hexanes to afford 342 as a colorless solid (0.428 g, 63%). ^1H NMR

(DMSO- d_6 , 400 MHz) δ 1.25 (d, 3H), 4.6 (m, 1H), 4.7 (s, 2H), 5.1 (s, 1H), 7.2 (d, 1H), 7.25 (d, 2H), 7.4 (d, 3H), 7.5 (t, 2H), 7.6 (m, 2H), 7.8 (d, 2H), 9.7 (s, 1H); MS (ES⁻) m/z 408 (M-H)⁻.

5 The racemic mixture was separated to give 2 enantiomers using the following conditions: an OJ chiral column, 22% IPA, 2 mL/min., 26°C, 3000 psi on SFC. Enantiomer 1 eluted at 9.214 min. to give an off-white solid 342-A (0.092 g, 14%). Enantiomer 2 eluted at 11.118 min. to give another off-white solid 342-B (0.059 g, 9%). The enantiomeric purity was found to be >99% and the absolute stereochemistry were not determined.

Example 143



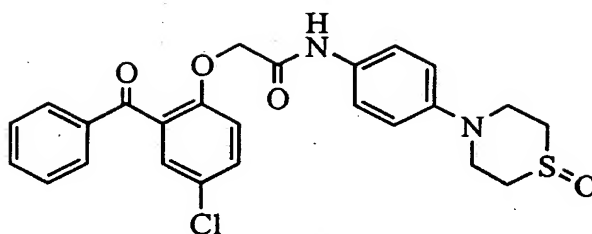
343

15 3-Chloroperoxybenzoic acid (~60%, 0.54 g, 1.9 mmol) was added portionwise to a solution of compound 332 (0.4 g, 0.86 mmol) in methylene chloride (30 mL) and stirred at rt. After 4 days, filtered the suspension and washed the solids with methylene chloride.

20 The filtrate was washed with saturated sodium meta bisulfite, 10% NaOH, and water. The organics were dried over MgSO₄, and concentrated in vacuo. The product was purified by flash chromatography using 99:1 methylene chloride:methanol and further purified by TLC prep plate eluted with 99:1 methylene chloride:methanol to afford 343 as an off-white foam (0.062 g, 14%). ¹H NMR (CDCl₃, 300 MHz), δ 3.1 (t, 4H), 3.8 (t, 4H), 4.7 (s, 2H), 6.9 (d, 2H), 7.05 (d, 1H), 7.4 (s, 1H), 7.5-7.6 (m, 5H), 7.65 (t, 1H), 7.9 (d, 2H), 9.05 (s, 1H); MS (AP⁻) m/z 497 (M-H)⁻.

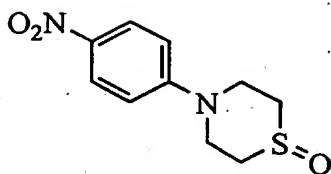
Example 144

231

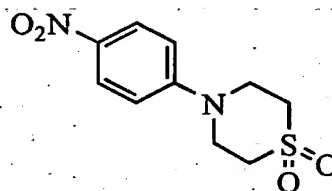


344

5 Step A:



345



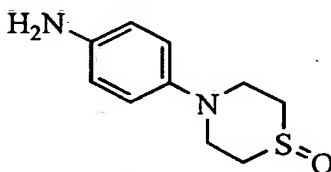
346

10

3-Chloroperoxybenzoic acid (~60%, 20.3 g, 70.6 mmol) in methylene chloride was added dropwise to a cooled solution of compound 333 (11.5 g, 51.1 mmol) in methylene chloride (250 mL total reaction volume) and stirred at -78 °C. After 2 h, the reaction was warmed to rt and stirred overnight. The reaction mixture was washed with saturated sodium meta

15 bisulfite, 2N NaOH, and water. The organics were separated, dried over MgSO₄, and concentrated in vacuo to give a mixture of 345 and 346 as a yellow solid (8.47 g, crude material). The crude material was used without purification.

Step-B:



347

20

The mixture of 345 and 346 (8.47 g, 35.3 mmol), palladium on carbon (1.4 g, 10% w/w), ethanol (100 mL) and THF (50 mL) were used as in general procedure XII using 60 psi of

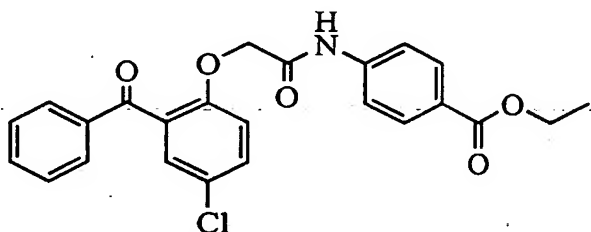
25 hydrogen. The product was purified by flash chromatography using a gradient between 4:1 and 9:2 hexanes:ethyl acetate to afford 347 as a yellow solid (3.94 g, 53.2 %). ¹H

NMR (DMSO- d_6 , 400 MHz) δ 2.7 (dd, 2H), 2.9 (m, 2H), 3.16 (dd, 2H), 3.7 (t, 2H), 4.6 (bs, 2H), 6.46 (dd, 2H), 6.71 (dd, 2H); MS (ES⁺) m/z 211 (M+H)⁺.

Step C:

Carboxylic acid 105 (4.15 g, 14.3 mmol), HCA (1.08 mL, 7.1 mmol), THF (60 mL), PPh₃ (1.82 g, 6.95 mmol) in THF (15 mL), sulfoxide 347 (3 g, 14.3 mmol) in THF (125 mL), and pyridine (15 mL, 185 mmol) were used as in general procedure XIII. The product was purified by flash chromatography using a gradient between 99:1 and 9:1 methylene chloride:methanol and further purified by triturating the resulting solid with methanol and ethanol, filtering, and washing the solids with water and methanol to afford 344 as a tan solid (2.7g, 39%). ¹H NMR (DMSO- d_6 , 300 MHz) δ 2.7 (d, 2H), 2.9 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.7 (s, 2H), 7 (d, 2H), 7.2 (d, 1H), 7.4 (d, 2H), 7.47 (s, 1H), 7.55 (d, 2H), 7.65 (t, 2H), 7.8 (d, 2H), 9.6 (s, 1H); MS (AP⁻) m/z 481 (M-H)⁻.

Example 145

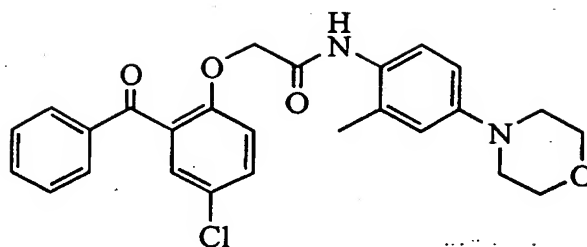


348

Glycerol-p-aminobenzoate (ICN, 0.342 g, 1.62 mmol), NEt₃ (0.25 mL, 1.79 mmol), acetonitrile (7 mL), and acid chloride 320 (0.5 g, 1.62 mmol) in acetonitrile (8 mL) were used as in general procedure X. The product was purified by flash chromatography using 9:1 hexanes:ethyl acetate then further purified by flash chromatography using 99:1 methylene chloride:methanol to afford 348 as an off-white solid (0.02 g, 3%). ¹H NMR (DMSO- d_6 , 300 MHz) δ 1.3 (t, 3H), 4.3 (q, 2H), 4.8 (s, 2H), 7.5 (d, 1H), 7.6 (d, 2H), 7.7 (d, 4H), 7.8 (d, 2H), 7.9 (d, 2H), 10.2 (s, 1H); MS (ES⁻) m/z 436 (M-H)⁻.

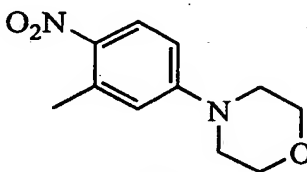
Example 146

233



349

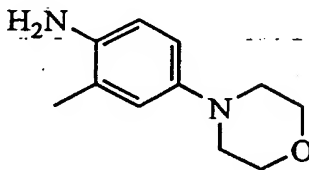
5 Step A:



350

4-Chloro-2-nitrotoluene (SALOR, 2 g, 11.7 mmol) in pyridine (25 mL), sodium bicarbonate (2 g, 23.8 mmol), water (5 mL), and morpholine (Aldrich, 2.03 g, 23.3 mmol) were used as in general procedure XI to afford 350 as a yellow solid (0.804 g, 31%). ¹H NMR (DMSO-d₆, 300 MHz) δ 2.5 (s, 3H), 3.4 (t, 4H), 3.7 (t, 4H), 6.9 (d, 2H), 8 (d, 1H). The crude material was used without purification.

Step B:



351

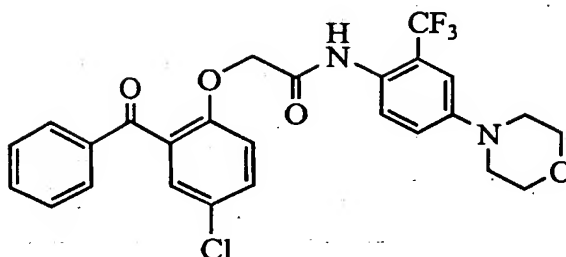
Compound 350 (0.72 g, 4.63 mmol), palladium on carbon (0.1 g, 10% w/w), ethanol (20 mL), and THF (20 mL) were used as in general procedure XII using 50 psi of hydrogen to afford 351 as a brown solid (0.623 g, crude material).

20 Step C:

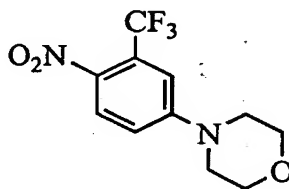
Compound 351 (0.623 g, 3.2 mmol), NEt₃ (1.3 mL, 9.3 mmol) in acetonitrile (8 mL), and acid chloride 320 (1.02 g, 3.3 mmol) in acetonitrile (7 mL) were used as in general procedure X. The product was purified by flash chromatography using 99.5:0.5 methylene chloride:methanol to afford 349 as an orange foam (0.072 g, 5%). ¹H NMR (DMSO-d₆, 400 MHz) δ 1.9 (s, 3H), 3 (t, 4H), 3.7 (t, 4H), 4.65 (s, 2H), 6.7 (d, 1H), 6.73 (s, 1H), 7.1

234

(d, 1H), 7.2 (d, 1H), 7.4 (s, 1H), 7.5 (t, 2H), 7.6 (t, 2H), 7.75 (d, 2H), 8.8 (s, 1H); MS (ES⁺) m/z 463 (M-H)⁺.

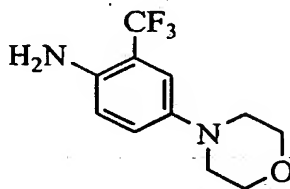
Example 147

352

Step A:

353

5-Bromo-2-nitrobenzotrifluoride (Lancaster, 2 g, 7.4 mmol) in pyridine (20 mL), sodium bicarbonate (1.25 g, 14.8 mmol), water (5 drops), and morpholine (Aldrich, 1.29 g, 14.8 mmol) were used as in general procedure XI to afford 353 as a yellow solid (1.62 g, 79%). ¹H NMR (DMSO-d₆, 400 MHz) δ 3.5 (t, 4H), 3.8 (t, 4H), 7.25 (d, 1H), 7.3 (s, 1H), 8.1 (d, 1H). The crude product was used without purification.

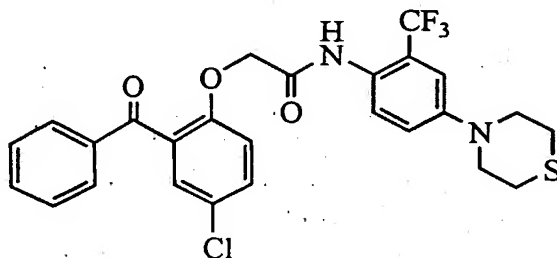
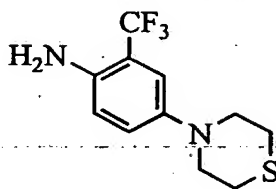
Step B:

354

Compound 353 (1.62 g, 5.9 mmol), palladium on carbon (0.2 g, 10% w/w), ethanol (12 mL) and THF (12 mL) were used as in general procedure XII using 75 psi of hydrogen to afford 354 as a brown solid (1.41 g, crude material).

Step C:

Compound **354** (1.41 g, 5.73 mmol), NEt₃ (0.8 mL, 5.74 mmol), acetonitrile (15 mL), and
5 acid chloride **320** (1.8 g, 5.82 mmol) in acetonitrile (15 mL) were used as in general
procedure X. The product was purified by flash chromatography using 35% ethyl acetate
in hexanes and further purified by flash chromatography using 1:1 ethyl acetate:hexanes to
afford **352** as an off-white solid (0.426 g, 14%). ¹H NMR (DMSO-d₆, 400 MHz) δ 3.2 (t,
4H), 3.75 (t, 4H), 4.7 (s, 2H), 7.15 (s, 1H), 7.2 (m, 3H), 7.45-7.55 (m, 3H), 7.6 (t, 2H), 7.8
10 (d, 2H), 9 (s, 1H); MS (ES⁺) *m/z* 517 (M-H⁺).

Example 148**355****Step A:****356**

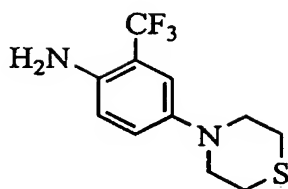
20

25

5-Bromo-2-nitrobenzotrifluoride (Lancaster, 2 g, 7.4 mmol) in pyridine (20 mL), sodium
bicarbonate (1.25 g, 14.9 mmol), water (5 drops), and thiomorpholine (Aldrich, 1.52 g,
14.7 mmol) were used as in general procedure XI to afford **356** as a yellow solid (1.63 g,
crude material). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.65 (t, 4H), 3.88 (t, 4H), 7.2 (d, 1H),
7.22 (s, 1H), 8 (d, 1H).

Step B:

236



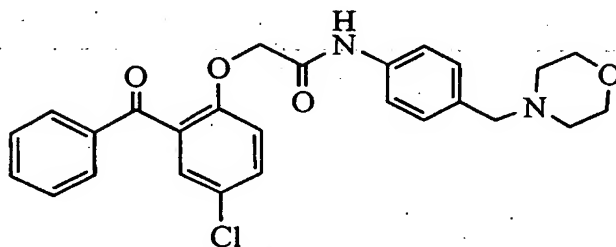
357

Compound **356** (1.63 g, 5.6 mmol), palladium on carbon (0.3 g, 10% w/w), ethanol (12 mL) and THF (12 mL) were used as described in general procedure XII using 75 psi of hydrogen to afford **357** as a brown oil (1.29 g, 88%). The crude material was used without purification.

Step C:

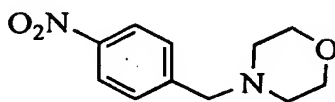
Compound **357** (1.29 g, 4.92 mmol), NEt₃ (0.7 mL, 5.02 mmol), acetonitrile (15 mL), and acid chloride **320** (1.52 g, 4.92 mmol) in acetonitrile (15 mL) were used as in general procedure X. The product was purified by flash chromatography using 35% ethyl acetate in hexanes to afford **355** as an orange oil (0.264 g, 10%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.62 (m, 4H), 3.57 (m, 4H), 4.68 (s, 2H), 7.07 (d, 1H), 7.16 (q, 3H), 7.41 (d, 1H), 7.45 (m, 3H), 7.58 (m, 2H), 7.75 (d, 2H), 9 (s, 1H); MS (ES⁺) *m/z* 533 (M-H)⁺.

Example 149



358

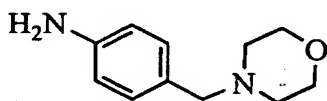
Step A:



359

237

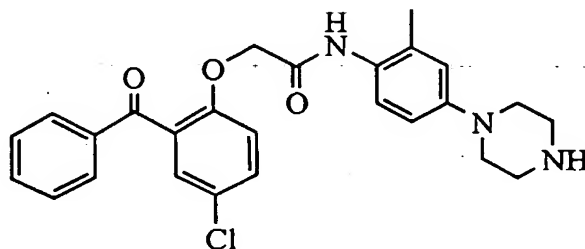
Morpholine (Aldrich, 0.74 mL, 8.5 mmol) was added dropwise to a solution of 4-nitrobenzylbromide (Aldrich, 2 g, 9.26 mmol), in acetone (20 mL), and potassium carbonate (2.4 g, 17.4 mmol). The resulting suspension was stirred at rt for 6 d under nitrogen. The mixture was filtered and the filtrate was concentrated in vacuo to afford **359** as a pale yellow solid (1.89 g, crude material).

Step B:**360**

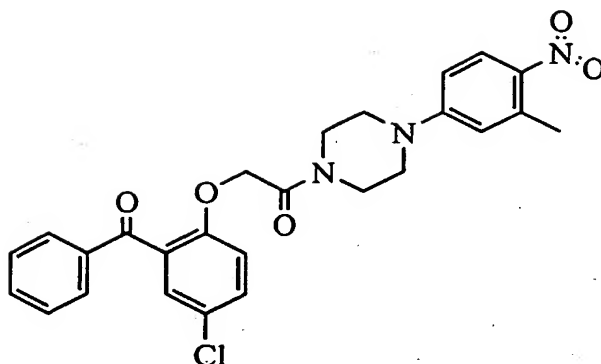
Compound **359** (1.89 g, 4.63 mmol), palladium on carbon (0.325 g, 10% w/w), ethanol (25 mL) and THF (25 mL) were used as in general procedure XII using 50 psi of hydrogen to afford **360** as a brown solid (1.6 g, crude material).

Step C:

Compound **360** (1.6 g, 8.3 mmol), NEt₃ (0.95 mL, 6.8 mmol), acetonitrile (7 mL), and acid chloride **320** (1.53 g, 4.95 mmol) in acetonitrile (7 mL) were used as in general procedure X. The product was purified by flash chromatography using a gradient between 9:1 and 4:1 hexanes:ethyl acetate to afford **358** as an off-white solid (0.264 g, 12%). ¹H NMR (DMSO-d₆, 300 MHz) δ 2.35 (d, 4H), 3.41 (s, 3H), 3.57 (t, 4H), 4.73 (s, 2H), 7.23 (m, 3H), 7.47-7.67 (m, 7H), 7.83 (d, 2H), 9.78 (s, 1H); MS (ES⁺) m/z 463 (M-H).

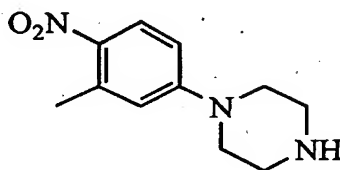
Example 150 and Example 151**361**

238



362

5 Step A:

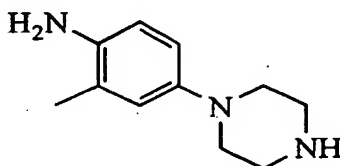


363

4-Chloro-2-nitrotoluene (SALOR, 1.46 g, 8.5 mmol) in pyridine (5 mL) was added dropwise to a solution of pyridine (22 mL), sodium bicarbonate (0.73 g, 8.7 mmol), piperazine (Aldrich, 1.5 g, 17.4 mmol), and water (3 mL) and the resulting mixture was refluxed for 2 d under nitrogen. Additional piperazine (1.5 g, 17.4 mmol) and sodium bicarbonate (0.73 g, 8.7 mmol) were added and the mixture was refluxed overnight. Acetone (200 mL) was added to the mixture and it was filtered hot. Water was added to the filtrate and the mixture was cooled to rt. Filtered the resulting suspension and concentrated the filtrate in vacuo. The concentrate was dissolved in hot methanol and ether and cooled to rt. The resulting mixture was filtered and the filtrate was concentrated in vacuo to afford 363 as a yellow solid (4.22 g). MS (ES⁺) *m/z* 222 (M+H)⁺. The crude product was used without purification.

20

Step B:



239

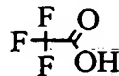
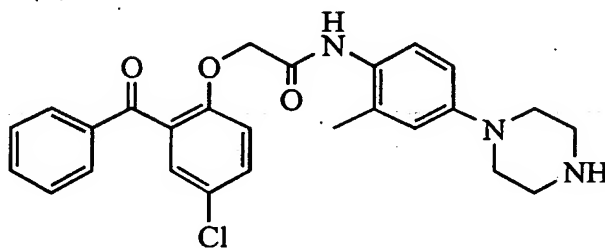
364

Compound **363** (1.88 g, 8.5 mmol), palladium on carbon (0.563 g, 10% w/w), ethanol (35 mL), and THF (35 mL) were used as in general procedure XII to afford **364** as a yellow oil (1.7 g). The crude product was used without purification.

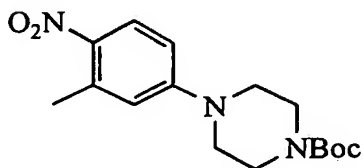
Step C:

Compound **364** (1.7 g, 8.9 mmol), NEt₃ (1.4 mL, 10 mmol), acetonitrile (12 mL), and acid chloride **320** (2.36 g, 7.6 mmol) in acetonitrile (12 mL) were used as in general procedure X. Water was added to the reaction mixture and the resulting suspension was filtered.

The filtrate was partitioned between 2N NaOH and ethyl acetate. The aqueous layer was acidified with 1N sodium hydrogen sulfate to pH 1 and extracted with ethyl acetate. The product was purified by flash chromatography using a gradient between 3:2 hexanes:ethyl acetate, ethyl acetate, and methanol to afford **362** as a yellow solid (0.250 g) MS (ES⁺) *m/z* 494 (M+H)⁺ and **361** as an orange solid (0.005g, 0.1%). ¹H NMR (DMSO-d₆, 400 MHz) δ 1.96 (s, 3H), 2.79 (m, 4H), 2.97 (m, 4H), 4.66 (s, 2H), 6.66 (m, 2H), 7.05 (d, 1H), 7.2 (d, 1H), 7.42 (d, 1H), 7.46 (t, 2H), 7.6 (t, 2H), 7.75 (d, 2H), 8.79 (s, 1H); MS (ES⁺) *m/z* 464 (M+H)⁺.

Example 152

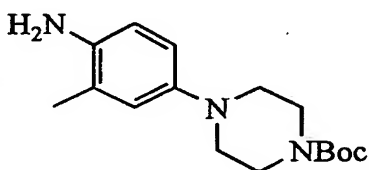
365

Step A:

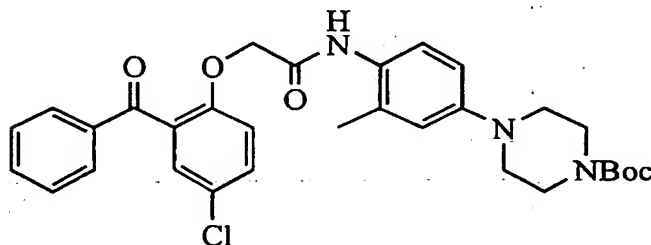
240

366

5-Fluoro-2-nitrotoluene (Aldrich, 2 g, 12.9 mmol) in pyridine (5 mL) was added dropwise to a solution of pyridine (15 mL), sodium bicarbonate (1.62 g, 19.3 mmol), 1-t-butoxycarbonyl piperazine (Aldrich, 3.6 g, 19.3 mmol), and water (1.2 mL) and the resulting mixture was refluxed overnight. Acetone was added to the reaction and the resulting mixture was filtered hot. Water was added and the mixture was cooled to rt. The resulting solid was filtered and washed with water and ether to afford **366** as an orange solid (4.02 g). ¹H NMR (DMSO-d₆, 400 MHz) δ 1.39 (s, 9H), 2.47 (s, 3H), 3.41 (s, 8H), 6.84 (m, 2H), 7.97 (d, 1H). The crude material was used without purification.

Step B:**367**

Compound **366** (4.02 g, 12.5 mmol), palladium on carbon (1.2 g, 10% w/w), ethanol (90 mL) and THF (10 mL) were used as in general procedure XII using 80 psi of hydrogen. The product was filtered through a celite pad eluted with 9:1 methylene chloride:methanol and concentrated in vacuo to afford **367** as a pink solid (2.926 g, crude material).

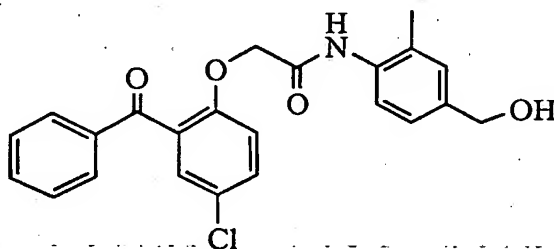
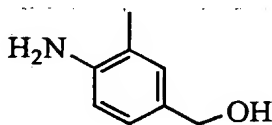
Step C:**368**

Acid chloride **320** in methylene chloride was added dropwise to a solution of compound **367** (0.362 g, 1.24 mmol) in pyridine (20 mL) and stirred for 2 days. The reaction was concentrated in vacuo, ethanol and ice were added, and the resulting solid was filtered and washed with ether to afford **368** as a yellow solid (0.118 g, 20.2%). ¹H NMR (DMSO-d₆,

400 MHz) δ 1.38 (d, 9H), 1.95 (s, 3H), 3 (d, 4H), 3.4 (s, 4H), 4.67 (s, 2H), 6.7 (m, 2H), 7.1 (d, 1H), 7.42 (d, 1H), 7.48 (m, 2H), 7.6 (m, 2H), 7.75 (d, 2H), 8.8 (s, 1H).

Step D:

TFA (15 mL, 195 mmol) was added to a solution of compound **368** (0.118 g, 0.21 mmol) in acetonitrile and stirred overnight. The reaction mixture was concentrated in vacuo after carbon tetrachloride was added to azeotrope off the TFA. This procedure was repeated multiple times. The mixture was concentrated in vacuo to afford **365** as a yellow solid (0.085 g, 88%). ^1H NMR (DMSO- d_6 , 400 MHz) δ 1.96 (s, 3H), 3.08 (d, 4H), 3.17 (d, 4H), 4.67 (s, 2H), 6.72 (m, 2H), 7.1 (d, 1H), 7.2 (d, 1H), 7.42 (s, 1H), 7.46 (m, 2H), 7.6 (m, 2H), 7.75 (d, 2H), 8 (bs, 1H), 8.86 (s, 1H); MS (ES $^+$) m/z 464 (M+H) $^+$.

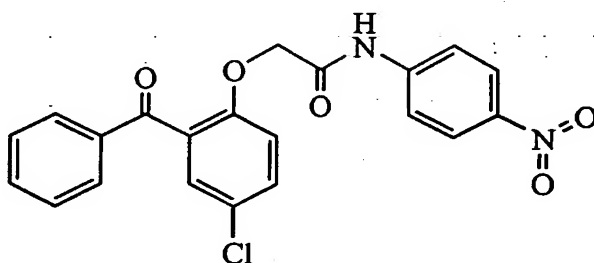
Example 153**369****Step A:****370**

3-Methyl-4-nitrobenzyl alcohol (Aldrich, 1g, 5.98 mmol), palladium on carbon (0.265 g, 10% w/w), ethanol (12 mL), and THF (12 mL) were used as in general procedure XII using 58 psi hydrogen to afford **370** as a yellow oil (0.65 g, 79%). The crude material was used without purification.

Step B:

Compound **370** (0.65 g, 4.74 mmol), NEt_3 (0.95 mL, 6.82 mmol), acetonitrile (10 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (10 mL) were used as in general procedure X. The product was purified by flash chromatography using 1:1 hexanes:ethyl acetate to afford **369** as a yellow solid (0.041 g, 2.1%). ^1H NMR (DMSO-d_6 , 400 MHz) δ 2 (s, 3H), 4.4 (s, 2H), 4.7 (s, 2H), 5.1 (bs, 1H), 7.1 (m, 2H), 7.25 (m, 2H), 7.45 (m, 3H), 7.6 (m, 2H), 7.76 (d, 2H), 8.9 (s, 1H); MS (ES^-) m/z 408 (M-H^-).

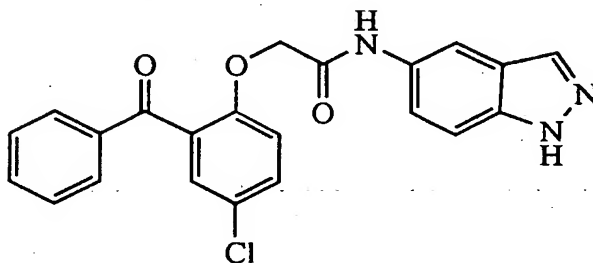
Example 154



371

4-Nitroaniline (Sigma, 0.244 g, 1.77 mmol), NEt_3 (0.25 mL, 1.79 mmol), acetonitrile (5 mL), and acid chloride **320** (0.54 g, 1.75 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using 4:1 hexanes:ethyl acetate to afford **371** as an off-white solid (0.012 g, 2%). ^1H NMR (CDCl_3 , 300 MHz) δ 4.8 (s, 2H), 7.05 (d, 1H), 7.4 (d, 1H), 7.5 (m, 3H), 7.65 (t, 1H), 7.9 (d, 2H), 8 (d, 2H), 8.25 (d, 2H), 10 (s, 1H); MS (ES^-) m/z 409 (M-H^-).

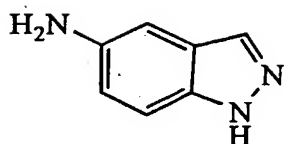
Example 155



372

Step A:

243



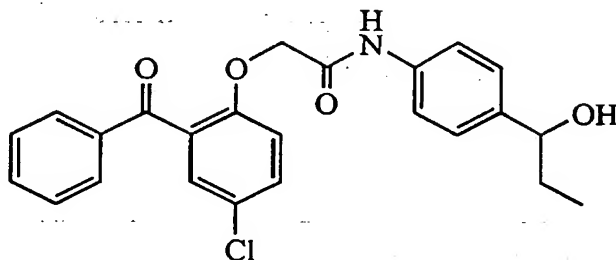
373

5-Nitroindazole (Aldrich, 1.2 g, 7.36 mmol), palladium on carbon (0.23 g, 10% w/w), ethanol (25 mL), and THF (5 mL) were used as in general procedure XII using 78 psi of hydrogen to afford **373** as a pink solid (0.98 g, crude material). ¹H NMR (DMSO-d₆, 400 MHz) δ 4.7 (s, 2H), 6.7 (dd, 2H), 7.2 (d, 1H), 7.7 (s, 1H), 12.5 (s, 1H).

Step B:

Compound **373** (1 g, 7 mmol), NEt₃ (1.2 mL, 8.6 mmol), acetonitrile (20 mL), and acid chloride **320** (1.9 g, 6.2 mmol) in acetonitrile (10 mL) were used as in general procedure X. Ice water was added and the resulting suspension was filtered, washed with water, and the solid was recrystallized from ethanol and water. The resulting precipitate was filtered and washed with ether to afford **372** as a pink solid (0.679 g, 17.3%). ¹H NMR (DMSO-d₆, 400 MHz) δ 4.7 (s, 2H), 7.2 (d, 1H), 7.3 (d, 1H), 7.4-7.5 (m, 4H), 7.55-7.6 (m, 2H), 7.6 (dd, 2H), 8 (s, 2H), 9.7 (s, 1H), 13 (s, 1H); MS (ES⁻) *m/z* 406 (M-H).

Example 156

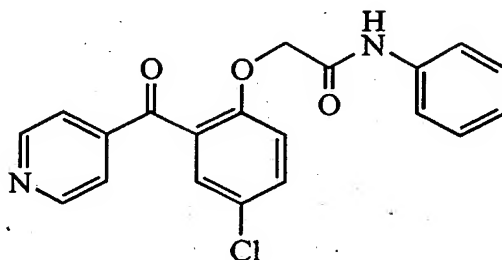


374

4-Aminophenyl ethyl carbinol (Apin, 0.254 g, 1.7 mmol), NEt₃ (0.28 mL, 2 mmol), acetonitrile (6 mL), and acid chloride **320** (0.53 g, 1.7 mmol) in acetonitrile (6 mL) were used as in general procedure X. The mixture was filtered, washed with 1M sodium hydrogen sulfate, and the filtrate was extracted with ethyl acetate. The organics were

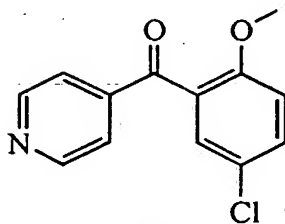
separated, dried over MgSO_4 , and concentrated in vacuo. The product was purified by flash chromatography using 93:7 methylene chloride:methanol, flash chromatography using 95:5 methylene chloride:methanol, a TLC prep plate using 92:8 methylene chloride:methanol, and a TLC prep plate using 9:1 methylene chloride:methanol to afford 374 as an off-white solid (0.029 g, 4%). ^1H NMR (DMSO-d_6 , 300 MHz) δ 0.8 (t, 3H), 1.6 (m, 2H), 4.4 (m, 1H), 4.7 (s, 2H), 5.08 (d, 1H), 7.2 (t, 3H), 7.47 (d, 3H), 7.55 (m, 2H), 7.65 (m, 2H), 7.85 (d, 2H), 9.7 (s, 1H); MS (ES $^-$) m/z 422 (M-H).

Example 157



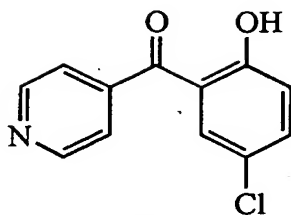
375

Compound 378 (0.143 g, 0.64 mmol) was added to a solution of compound 377 (0.15 g, 0.64 mmol), potassium carbonate (0.09 g, 0.65 mmol), and DMF (5 mL) and stirred overnight. The mixture was poured into ice water, filtered, and the resulting solid was washed with ether. The product was purified by TLC prep plate using 23:1 methylene chloride:methanol to afford 375 as an orange solid (0.021g, 9%). ^1H NMR (DMSO-d_6 , 300 MHz) δ 4.7 (s, 2H), 7.06 (t, 1H), 7.25 (d, 1H), 7.3 (t, 2H), 7.55 (d, 2H), 7.58 (s, 1H), 7.67 (m, 3H), 8.77 (d, 2H) 9.86 (s, 1H); MS (ES $^-$) m/z 366 (M-H).



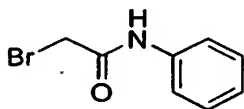
376

245



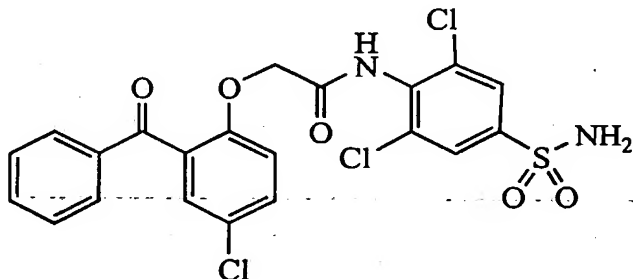
377

Compound **376** (4.2g, 17 mmol) in methylene chloride (100 mL), THF (100 mL), and BBr_3 (17g, 68 mmol) in methylene chloride (68 mL) were used as in general procedure IX to afford, after recrystallization from methanol, **377** as a yellow solid (1.1g, 28%). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 7 (d, 1H), 7.6 (d, 2H), 8.2 (d, 2H), 9.7 (bs, 2H), 10.95 (s, 1H); MS (ES^-) m/z 232 ($\text{M}-\text{H}$).



378

Example 158

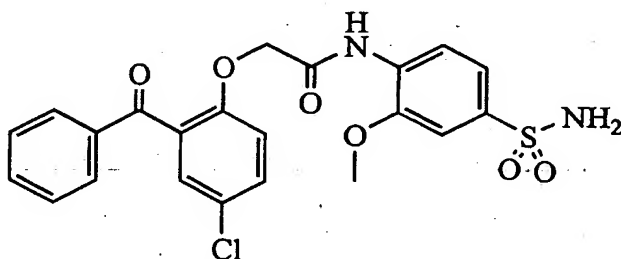


379

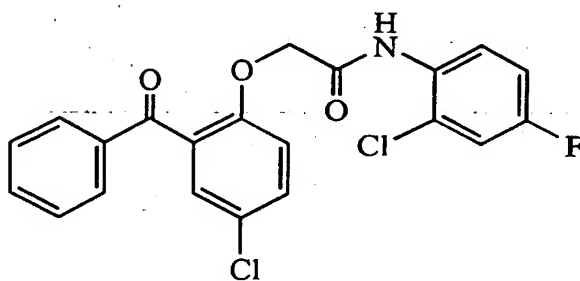
3,5-Dichloro sulfanilamide (Lancaster, 0.5 g, 2.1 mmol), NEt_3 (0.25 mL, 1.8 mmol), acetonitrile (10 mL), and acid chloride **320** (0.52 g, 1.7 mmol) in acetonitrile (6 mL) were used as in general procedure X. The reaction was heated to 40°C and stirred for 3 d. Additional acid chloride **320** (0.52 g, 1.7 mmol) was added and the reaction was stirred for 7 d. The mixture was concentrated in vacuo, suspended in methylene chloride, filtered, and the filtrate was concentrated in vacuo. The product was purified by flash chromatography using 99:1 methylene chloride:methanol, by flash chromatography in a gradient between 1:1 and 9:1 ethyl acetate:hexanes, and by TLC prep plate using 23:1 methylene chloride:methanol, 7:3 ethyl acetate:hexanes, and 98:2 methylene chloride:methanol as elutant to afford **379** as an orange oil (0.038 g, 4.3%). ^1H NMR

(DMSO- d_6 , 300 MHz) δ 4.56 (s, 2H), 6.57 (bs, 2H), 6.94 (d, 1H), 7.36 (s, 1H), 7.4 (m, 3H), 7.55 (m, 3H), 7.7 (d, 2H), 12.15 (bs, 1H); MS (ES⁺) m/z 512 (M-H)⁻.

5

Example 159**380**

10 3-Methoxy-4-amino sulfanilamide (Pfaltz Bauer, 0.5 g, 2.5 mmol), acetonitrile (16 mL), Et₃N (0.41 mL, 2.9 mmol), and acid chloride **320** (0.76 g, 2.5 mmol) in acetonitrile were used as in general procedure X. The reaction mixture was filtered and the resulting solids were washed with acetonitrile and ether to afford **380** as an off-white solid (0.169 g, 14.4 %). ¹H NMR (DMSO- d_6 , 400 MHz) δ 3.8 (s, 3H), 4.8 (s, 2H), 7.15 (d, 1H), 7.22 (d, 3H),
15 7.48 (m, 4H), 7.58 (d, 2H), 7.78 (d, 2H), 8.5 (s, 1H), 8.9 (s, 1H); MS (ES⁺) m/z 575 (M+H)⁺.

Example 160**381**

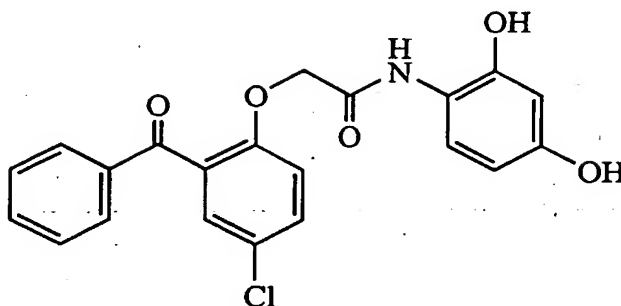
20

Acid chloride **320** (0.68 g, 2.2 mmol) in methylene chloride (5 mL) was added to a solution of 2-chloro-4-fluoroaniline (Aldrich, 0.5 g, 3.4 mmol), pyridine (12 mL) and the mixture was stirred overnight. The reaction mixture was poured over ice, ethanol (30 mL)
25 was added, and the precipitate was filtered and washed with 1:1 ethanol:water and diethyl ether to afford **381** as a white solid (0.367 g, 40%). ¹H NMR (DMSO- d_6 , 300 MHz) δ 4.8

(s, 2H), 7.25 (m, 2H), 7.5 (m, 9H), 7.65 (t, 2H), 7.75 (m, 1H), 7.8 (d, 2H), 9.2 (s, 1H); MS (ES⁺) *m/z* 419 (M+H)⁺.

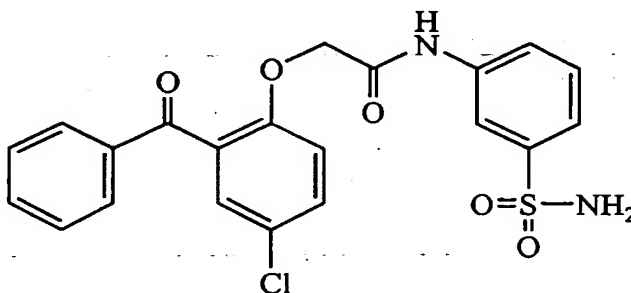
Example 161

5

**382**

Resorcinol hydrochloride (Aldrich, 0.5 g, 3.4 mmol), acetonitrile (20 mL total reaction volume), Et₃N (0.75 mL, 5.4 mmol), and acid chloride **320** (0.8 g, 2.6 mmol) in
10 acetonitrile were used as in general procedure X. The reaction mixture was poured over ice water and ethanol was added to the solution. The mixture was recrystallized from ethanol and water and the resulting solids were filtered and washed with ether to afford
382 as a pink solid (0.207 g, 20%). ¹H NMR (DMSO-d₆, 400 MHz) δ 4.6 (s, 2H), 6.1 (d,
15 1H), 6.28 (s, 1H), 7.19 (d, 1H), 7.4 (m, 4H), 7.56 (t, 2H), 7.75 (d, 2H), 8.5 (s, 1H), 9.1 (s, 1H), 9.6 (s, 1H); MS (ES⁺) *m/z* 398 (M+H)⁺.

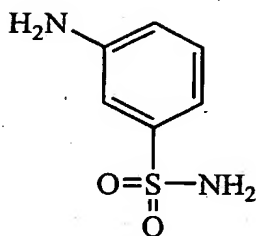
Example 162

**383**

20

Step A:

248

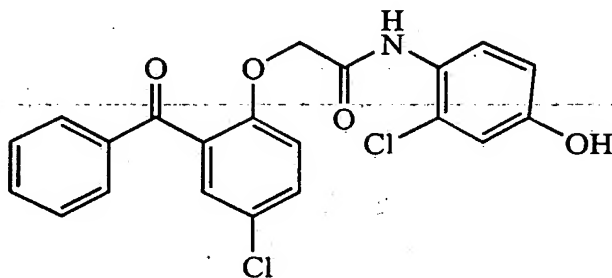


384

3-nitrobenzene sulfonamide (5 g, 24.7 mmol), palladium on carbon (1 g, 10% w/w), methanol (75 mL), and THF (25 mL) were used as in general procedure XII using 67 psi of hydrogen to afford **384** as a solid (4.2 g). ¹H NMR (DMSO-d₆, 400 MHz) δ 5.48 (bs, 2H), 6.67 (dd, 1H), 6.88 (d, 1H), 6.97 (t, 1H), 7.12 (t, 3H); MS (AP⁺) *m/z* 173 (M+H)⁺.

Step B:

Carboxylic acid **105** (0.29 g, 1 mmol), HCA (0.132 mL, 0.5 mmol), THF, PPh₃ (0.26 g, 1 mmol) in THF, metanilamide **384** (0.17 g, 1 mmol) in THF (4.5 mL total reaction volume), and pyridine (0.5 mL, 6.2 mmol) were used as in general procedure XIII. The reaction was concentrated in vacuo and the resulting solid was recrystallized from ethanol and water, filtered, and washed with ether to afford **383** as an off-white solid (0.207 g, 47%). ¹H NMR (DMSO-d₆, 400 MHz) δ 4.7 (s, 2H), 7.15 (d, 1H), 7.36 (s, 2H), 7.4-7.5 (m, 5H), 7.58 (m, 3H), 7.77 (d, 2H), 8.1 (s, 1H), 10.1 (s, 1H); MS (ES⁺) *m/z* 445 (M+H)⁺.

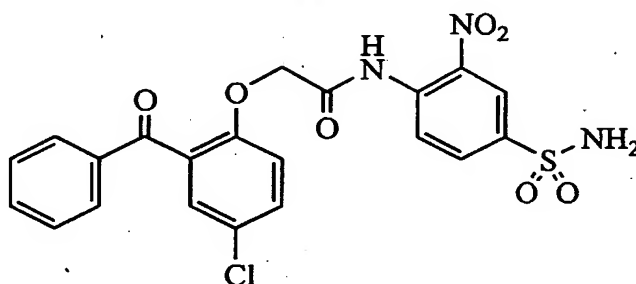
Example 163

385

Carboxylic acid **105** (0.29 g, 1 mmol), HCA (0.08 mL, 0.53 mmol), methylene chloride (5 mL total reaction volume), and PPh₃ (0.26 g, 1 mmol) were combined in a round-bottom flask under nitrogen at -78°C. 4-Amino-3-chlorophenol (Aldrich, 0.145 g, 1 mmol) was free-based by partitioning it between methylene chloride and saturated sodium bicarbonate. The organics were separated, dried over MgSO₄, and concentrated in vacuo

to give a pink solid that was dissolved in methylene chloride and Et₃N (0.26 mL, 1.9 mmol) and added dropwise to the reaction mixture at -78°C. The reaction was warmed to rt and concentrated in vacuo. The product was purified by flash chromatography using 4:1 hexanes:ethyl acetate to afford **385** as an orange solid (0.120 g, 29%). ¹H NMR (DMSO-d₆, 400 MHz) δ 4.7 (s, 2H), 6.67 (d, 1H), 6.79 (s, 1H), 7.2 (d, 1H), 7.35 (d, 1H), 7.4 (s, 1H), 7.5 (m, 2H), 7.6 (m, 2H), 7.75 (d, 2H), 8.9 (s, 1H), 9.8 (s, 1H); MS (ES⁺) *m/z* 417 (M+H)⁺.

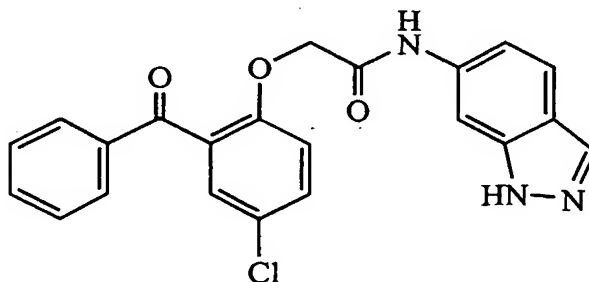
Example 164



386

Carboxylic acid **105** (0.67 g, 2.3 mmol), HCA (0.17 mL, 1.1 mmol), THF, PPh₃ (0.61 g, 2.3 mmol) in THF, 2-nitro-4-sulfanilamide (0.5 g, 2.3 mmol) in THF (20 mL total reaction volume), and pyridine (2.25 mL, 28 mmol) were used as in general procedure XIII. The reaction mixture was concentrated in vacuo and the product was purified by flash chromatography using a gradient between 9:1 hexanes:ethyl acetate and ethyl acetate to afford **386** as an off-white solid MS (ES⁻) *m/z* 488 (M-H)⁻.

Example 165

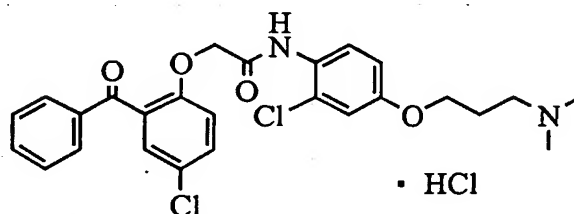


387

Carboxylic acid **105** (0.58 g, 2 mmol), HCA (0.152 mL, 1 mmol), THF, PPh₃ (0.52 g, 2 mmol) in THF, 6-aminoindazole (Aldrich, 0.26 g, 2 mmol) in THF (20 mL total reaction

volume), and pyridine (1.94 mL) were used as in general procedure XIII. The reaction mixture was concentrated in vacuo and the resulting solid was dissolved in ethanol. Water was added to the mixture and the resulting solid was filtered and washed with ether to afford **387** as a pink solid (0.309 g, 38%). ¹H NMR (DMSO-d₆, 400 MHz) δ 4.7 (s, 2H), 6.95 (d, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 7.5 (m, 2H), 7.55-7.65 (m, 3H), 7.79 (d, 2H), 7.9 (s, 1H), 8 (s, 1H), 9.89 (s, 1H), 12.85 (bs, 1H); MS (ES⁺) *m/z* 406 (M+H)⁺.

Example 166

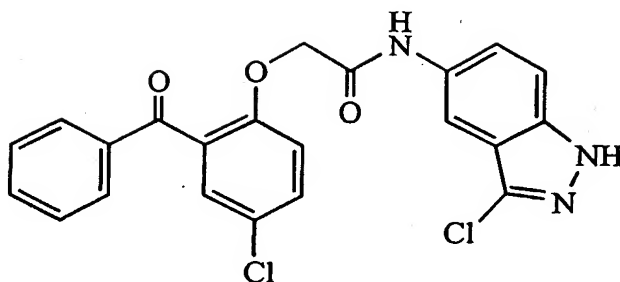


388

N,N-dimethyl-3-chloropropyl amine in acetone (5 mL) and water (4 drops) was added dropwise to a suspension of compound **385** (1.04 g, 2.5 mmol), acetone (10 mL), and potassium carbonate (2.82 g, 20.4 mmol) and then refluxed for 3 d under nitrogen. The suspension was cooled to rt and water and brine were added. The mixture was extracted with methylene chloride. To the organic layer was added 1N HCl in Et₂O (3 mL) and the resulting solution was concentrated in vacuo. The concentrate was purified by flash chromatography using a gradient between 9:1 and 4:1 methylene chloride:methanol as elutant to give an oil. The oil was dissolved in methylene chloride and 1N HCl in Et₂O (3 mL) was added and the mixture was stored at rt for 7 d. The precipitate was filtered and washed with ether to afford **388** as a yellow orange solid (0.125 g, 10%). ¹H NMR (DMSO-d₆, 300 MHz) δ 1.8 (m, 2H), 2.28 (s, 6H), 2.5 (m, 2), 4 (t, 2H), 4.8 (s, 2H), 6.9 (d, 1H), 7.08 (d, 1H), 7.25 (d, 1H), 7.45-7.58 (m, 4H), 7.65 (m, 2H), 7.8 (d, 2H), 9.05 (s, 1H); MS (ES⁺) *m/z* 502 (M+H)⁺.

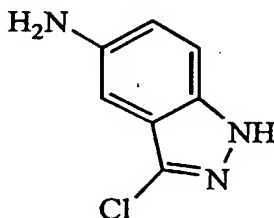
Example 167

251



389

5

Step A:

390

10

3-Chloro-5-nitroindazole (Lancaster, 5 g, 25 mmol), sodium dithionite (17.6 g, 101 mmol), ethanol (150 mL), and water (50 mL) were combined in a round-bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand and then refluxed overnight. The reaction mixture was concentrated in vacuo and the resulting solid was dissolved in ethyl acetate, washed with brine and water. The organics were separated, dried over MgSO_4 , and concentrated in vacuo to give **390** as a yellow solid (1.3 g, 31%). ^1H NMR (DMSO-d_6 , 400 MHz) δ 5. (s, 2H), 6.55 (s, 1H), 6.8 (d, 1H), 7.2 (s, 1H), 12.7 (s, 1H); MS (ES^+) m/z 168 ($\text{M}+\text{H}$) $^+$. The crude product was used without further purification.

15

20

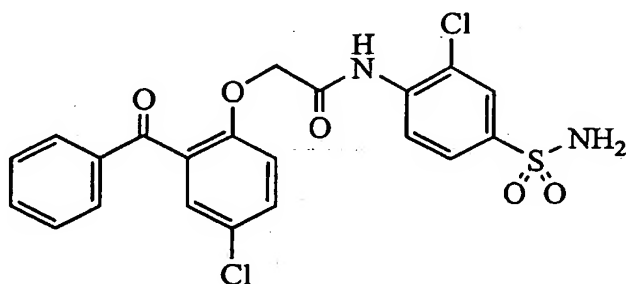
Step B:

Carboxylic acid **105** (2.25 g, 7.74 mmol), HCA (0.59 mL, 3.88 mmol), THF, PPh_3 (2.03 g, 7.74 mmol) in THF, compound **390** (1.3 g, 7.7 mmol) in THF (45 mL total reaction volume), and pyridine (7.5 mL, 93 mmol) were used as in general procedure XIII. The reaction mixture was concentrated in vacuo and the resulting solid was suspended in ethanol, methanol, acetone, and water. The resulting solid was filtered off and recrystallized from ethyl acetate:hexanes. The precipitate was filtered and washed with

25

ether and 7:3 ethyl acetate:hexanes to afford **389** as a tan solid (0.87 g, 26%). ¹H NMR (DMSO-d₆, 400 MHz) δ 4.7 (s, 2H), 7.2 (d, 1H), 7.35 (d, 1H), 7.415 (s, 1H), 7.43-7.52 (m, 4H), 7.55-7.6 (m, 4H), 7.78 (m, 2H), 7.9 (s, 1H), 9.88 (s, 1H), 13.2 (s, 1H).

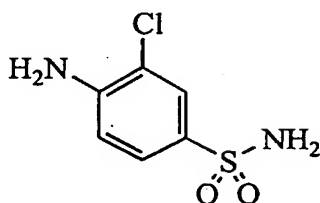
5 **Example 168**



391

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Step A:



392

15 Ammonium hydroxide (40 mL) was added to 3-chloro-4-aminosulfonyl fluoride (Maybridge, 0.5 g, 2.4 mmol) and the mixture was heated to 62 °C for 1 h under nitrogen. The reaction was cooled to rt and the resulting mixture was extracted with ethyl acetate. The organics were dried over MgSO₄ and concentrated in vacuo to give **392** as a white solid (0.394 g, 80%). ¹H NMR (DMSO-d₆, 400 MHz) δ 6.07 (s, 2H), 6.8 (d, 1H), 7 (s, 2H), 7.39 (dd, 1H), 7.55 (d, 1H); MS (ES⁻) *m/z* 205 (M-H)⁻.

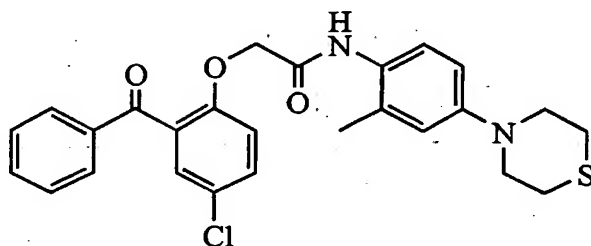
20

Step B:

25 Carboxylic acid **105** (0.54 g, 1.9 mmol), HCA (0.14 mL, 0.92 mmol), THF, PPh₃ (0.49 g, 1.9 mmol) in THF, compound **392** (0.384 g, 1.9 mmol), in THF (40 mL total reaction volume), and pyridine (1.8 mL) were used as in general procedure XIII. The reaction mixture was concentrated and the resulting solid was dissolved in ethanol. Water was

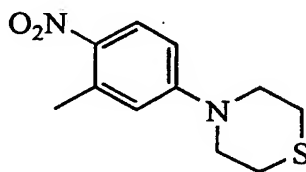
added and the precipitate was filtered and washed with 1:1 ethanol:water and ether to afford **391** as a white solid (0.206 g, 23.1%). ¹H NMR (DMSO-d₆, 400 MHz) δ 4.8 (s, 2H), 7.2 (d, 1H), 7.43 (s, 2H), 7.47 (m, 2H), 7.6 (m, 2H), 7.75 (dd, 3H), 7.8 (d, 1H), 8.05 (d, 1H), 9.3 (s, 1H).

Example 169



393

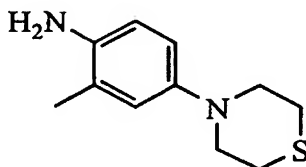
Step A:



394

5-Fluoro-2-nitrotoluene (Aldrich, 50.6 g, 364 mmol), DMSO (60 mL), and thiomorpholine (37 mL, 368 mmol) were combined and heated to 75°C for 2 h and 100°C for 4h under nitrogen. The reaction was cooled to rt. Ether was added to the mixture and the slurry was stirred vigorously. Water was added to the slurry and the resulting solid was filtered and washed with water and ether, then dissolved in methylene chloride. The organics were washed with water, dried over MgSO₄, and concentrated in vacuo to give **394** as a yellow solid (70 g, 81%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.5 (s, 3H), 2.6 (t, 4H), 3.8 (d, 1H), 6.85 (s, 1H), 7.95 (d, 1H). The crude product was used without further purification.

Step B:



254

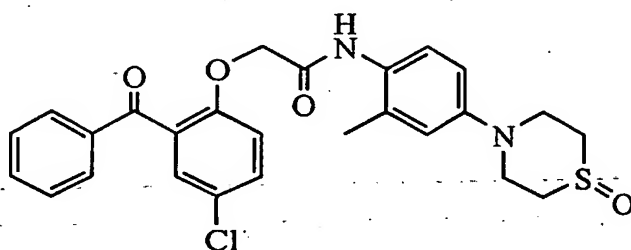
395

Compound 394 (0.29 g, 1.22 mmol), palladium on carbon (0.1 g, 10% w/w), ethanol (7 mL), and THF (7 mL) were used as in general procedure XII using 68 psi of hydrogen to afford 395 as a brown solid (0.252 g, crude material).

Step C:

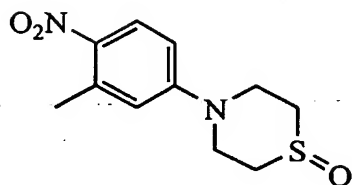
Compound 395 (0.252 g, 1.2 mmol), acetonitrile (12 mL), Et₃N (0.3 mL, 2.1 mmol), and acid chloride 320 (0.38 g, 1.2 mmol) were used as in general procedure X. The product was purified by flash chromatography using 7:3 hexanes:ethyl acetate as elutant to afford 393 as an orange solid (0.084 g, 14%). ¹H NMR (DMSO-d₆, 400 MHz) δ 1.95 (d, 3H), 2.6 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.67 (s, 2H), 6.75 (dd, 1H), 6.8 (d, 1H), 7.1 (d, 1H), 7.2 (d, 1H), 7.42 (d, 1H), 7.48 (t, 2H), 7.59 (t, 2H), 7.75 (d, 2H), 8.8 (s, 1H).

Example 170

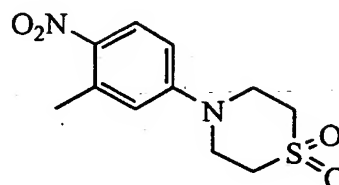


396

Step A:



397

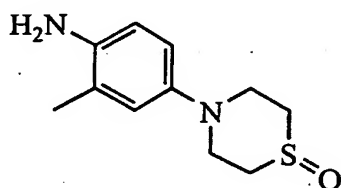


398

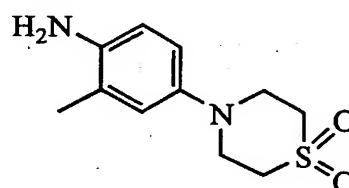
3-chloroperoxybenzoic acid (Aldrich, 0.046 g, 2.7 mmol) in methylene chloride was added dropwise to a stirred solution of compound 394 (12.5 g, 52.4 mmol) in methylene chloride (300 mL total volume for reaction) at -20 °C and the mixture was stirred for 1.5 h after

which the cooling bath was removed and the reaction was stirred at rt overnight under nitrogen. The mixture was washed with saturated sodium metabisulfite, 2N NaOH, and water. The organics were separated, dried over MgSO₄, and concentrated in vacuo to give a mixture of 397 and 398 as a yellow solid (12.2 g, crude mixture).

Step B:



399



400

The mixture of 397 and 398 (12.3 g), palladium on carbon (3.7 g, 10% w/w), ethanol (100 mL), THF (30 mL), and methanol (75 mL) were used as in general procedure XII using 60 psi of hydrogen to afford an oil. The product was purified on silica gel by flash

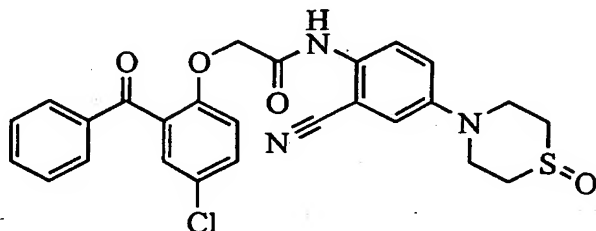
chromatography using 7:3 hexanes:ethyl acetate, 100% ethyl acetate, and 4:1 ethyl acetate:methanol as elutants to afford 399 as an orange solid (4.27 g, 39%) ¹H NMR (DMSO-d₆, 400 MHz) δ 1.99 (s, 3H), 2.68 (d, 2H), 2.87 (t, 2H), 3.15 (dd, 2H), 3.44 (t, 2H), 4.38 (bs, 2H), 6.49 (d, 1H), 6.59 (d, 1H), 6.64 (s, 1H); MS (ES⁺) *m/z* 225 (M+H)⁺ and 400 as a tan solid (3.57 g, 31%) ¹H NMR (DMSO-d₆, 400 MHz) δ 1.99 (s, 3H), 3.08 (m, 4H), 3.42 (m, 4H), 4.42 (bs, 2H), 6.49 (d, 1H), 6.59 (d, 1H), 6.66 (d, 1H); MS (ES⁺) *m/z* 241 (M+H)⁺.

Step C:

Carboxylic acid 105 (2.02 g, 6.95 mmol), HCA (0.528 mL, 3.48 mmol), THF (20 mL), PPh₃ (1.82 g, 6.95 mmol) in THF (15 mL), sulfoxide 399 (1.56 g, 6.95 mmol) in THF (125 mL total reaction volume), and pyridine (6.75 mL, 83.5 mmol) were used as in general procedure XIII. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The concentrate was purified by flash chromatography using a gradient between 99:1 and 4:1 methylene chloride:methanol as elutant to afford 396 as a yellow foam (1.62 g, 47%). ¹H NMR (DMSO-d₆, 400 MHz) δ 1.95 (d, 3H), 2.62 (dd, 2H), 2.86 (t, 2H), 3.5

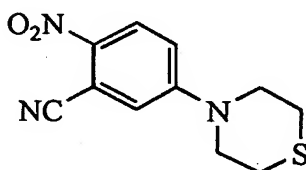
(dd, 2H), 3.69 (t, 2H), 4.67 (s, 2H), 6.75 (dd, 1H), 6.8 (d, 1H), 7.1 (d, 1H), 7.2 (d, 1H), 7.42 (d, 1H), 7.48 (t, 2H), 7.59 (t, 2H), 7.75 (d, 2H), 8.8 (s, 1H).

5 **Example 171**



401

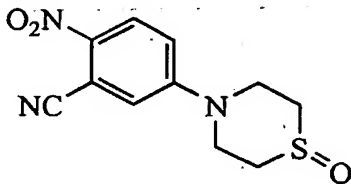
Step A:



402

5-Chloro-2-nitrobenzonitrile (Aldrich, 5 g, 27.4 mmol), sodium bicarbonate (4.62 g, 55 mmol), pyridine (40 mL), water (1 mL), and thiomorpholine (5.53 mL, 55 mmol) were used as in general procedure XI to afford **402** as an orange solid (5.19 g, 76%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.62 (m, 4H), 3.9 (m, 4H), 7.2 (d, 1H), 7.5 (d, 1H), 8.1 (d, 1H). The crude product was used without purification.

Step B:

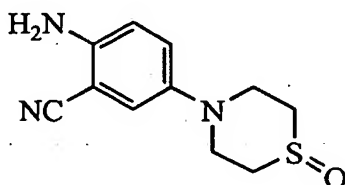


403

3-Chloroperoxybenzoic acid (Aldrich, 4.85 g, 17 mmol) in methylene chloride was added to a cooled solution of compound **402** (3 g, 12 mmol) in methylene chloride (100 mL total volume for reaction) at -20°C and the mixture was stirred for 15 min. after which the cooling bath was removed and the mixture was stirred at rt for 4 h under nitrogen. The

reaction mixture was washed with saturated sodium metabisulfite, 2N NaOH, and brine. The organics were separated, dried over MgSO_4 , and concentrated in vacuo to afford **403** as a yellow solid (0.59 g, crude material). ^1H NMR (DMSO-d_6 , 400 MHz) δ 2.63 (m, 4H), 3.9 (m, 4H), 7.2 (dd, 1H), 7.5 (d, 1H), 8.1 (d, 1H).

5

**404**

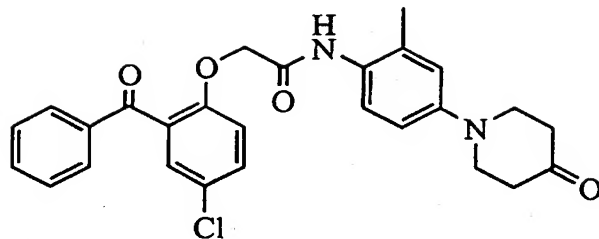
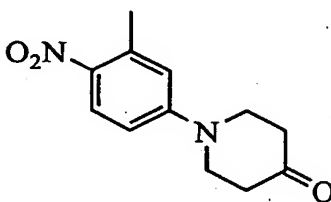
- 10 Palladium on carbon (0.23 g, 10% w/w), compound **403** (0.5 g, 1.9 mmol), ethanol (30 mL total reaction volume), THF (20 mL), and methanol (20 mL) were used as in general procedure XII to afford **404** as a green oil (0.41 g, 93%). ^1H NMR (DMSO-d_6 , 300 MHz) δ 2.68 (d, 2H), 2.9 (t, 2H), 3.3 (d, 2H), 3.55 (t, 2H), 5.6 (bs, 2H), 6.79 (d, 1H), 7.02 (d, 1H), 7.17 (dd, 1H).

15

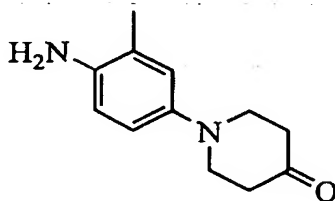
Step C:

- Compound **404** (0.41 g, 1.8 mmol), HCA (0.132 mL, 0.87 mmol), PPh_3 (0.46 g, 1.75 mmol), pyridine (1.7 mL, 21 mmol), THF (25 mL), and carboxylic acid **105** (0.51 g, 1.8 mmol) were used as in general procedure XIII. The concentrate was purified by flash chromatography using 95:5 methylene chloride:methanol as elutant, flash chromatography using a gradient between 7:3 hexanes:ethyl acetate and 4:1 ethyl acetate:methanol as elutant, TLC prep plate using 9:1 methylene chloride:methanol with 0.1% Et_3N as elutant. The concentrate was dissolved in methylene chloride and washed with 2N HCl. The
- 25 organics were separated, dried over MgSO_4 , and concentrated in vacuo to afford **401** as a tan foam (0.145 g, 16%). ^1H NMR (DMSO-d_6 , 300 MHz) δ 2.65 (d, 2H), 2.9 (t, 2H), 3.8 (m, 4H), 4.76 (s, 2H), 7.2 – 7.4 (m, 3H), 7.4 – 7.6 (m, 4H), 7.65 (m, 2H), 7.8 (d, 2H), 9.7 (s, 1H).

258

Example 172**405****Step A:****406**

4-Piperidone monohydrate monohydrochloride salt (Lancaster, 2.73 g, 17.8 mmol) and saturated potassium carbonate (10 mL) were combined in a round-bottom flask and stirred for 10 min. Pyridine (45 mL) and 2-nitro-5-fluorotoluene (Aldrich, 1.41 mL, 9.35 mmol) were added and the reaction was refluxed overnight. The two-phase solution was separated and the organics were concentrated in vacuo. The concentrate was dissolved in ethyl acetate and washed with water and brine. The organics were dried over MgSO_4 and concentrated in vacuo to afford **406** as a red oil (0.59 g, 27). ^1H NMR (DMSO-d_6 , 300 MHz) δ 2.6 (t, 4H), 3.8 (t, 4H), 7 (d, 2H), 8 (d, 2H); MS (ES^+) m/z 235 ($\text{M}+\text{H}$) $^+$.

Step B:**407**

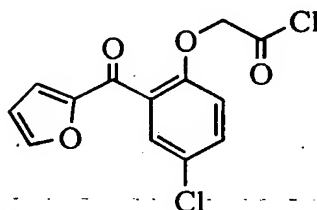
Compound **406** (0.57 g, 2.4 mmol), palladium on carbon (0.17 g, 10% w/w), ethanol (25 mL) and THF (25 mL) were used as in general procedure XII using 70 psi hydrogen to afford **407** as a yellow oil (0.5 g, crude material).

5 **Step C:**

Compound **407** (0.5 g, 2.1 mmol), HCA (0.16 mL, 1.05 mmol), PPh₃ (0.56 g, 2.1 mmol), pyridine (2 mL, 25 mmol), THF (50 mL), and carboxylic acid **105** (0.62 g, 2.1 mmol) were used as in general procedure XIII. The mixture was concentrated in vacuo and

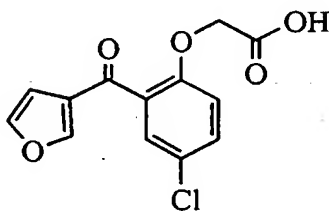
10 purified on by flash chromatography using a gradient between 1:1 hexanes:ethyl acetate and 100% ethyl acetate as elutant to afford **405** as a yellow solid (0.32 g, 31%). ¹H NMR (DMSO-d₆, 300 MHz) δ 2 (s, 3H), 2.4 (m, 4H), 3.58 (m, 4H), 4.7 (s, 2H), 6.85 (d, 1H), 6.9 (s, 1H), 7.15 (d, 1H), 7.25 (d, 1H), 7.48 (s, 1H), 7.55 (t, 2H), 7.65 (t, 2H), 7.8 (d, 2H), 8.85 (s, 1H); MS (ES⁺) *m/z* 478 (M+H)⁺.

15



408

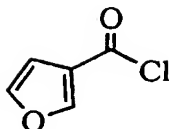
20 Carboxylic acid **115** (1 g, 3.6 mmol), methylene chloride (30 mL), and thionyl chloride (7.6 mL, 104 mmol) were used as in general procedure XV to afford **408** as a purple oil (1.24 g, crude material).



409

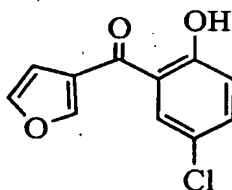
25 Ester **412** (15.92 g, 52 mmol), ethanol (EtOH, 150 mL), water (50 mL), and lithium hydroxide monohydrate (2.71 g, 65 mmol) were used as in general procedure IV to afford **409** as a tan solid (7.47 g, 51.6%). The crude material was used without purification.

260



410

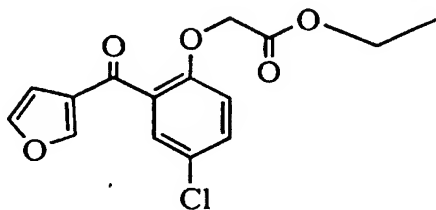
- 5 Thionyl chloride (60 mL, 800 mmol) was added portionwise to a solution of 3-furoic acid (11.21 g, 100 mmol) in methylene chloride (100 mL) and the mixture was refluxed for 2 h. The solution was concentrated in vacuo to afford the acid chloride 410 as an oil (13 g, crude material).



10

411

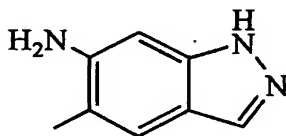
- Acid chloride 410 (13 g, 100 mmol), aluminum chloride (AlCl_3 , 13.6 g, 100 mmol), CH_2Cl_2 (200 mL), and 4-chloroanisole (12.25 mL, 100 mmol) were used as in general
15 procedure III. The product was purified by flash chromatography using a 7:3 hexanes:methylene chloride and 1:1 hexanes:methylene chloride as elutant. The concentrate was triturated between ether and hexanes, filtered, and the resulting solid was washed with hexanes to afford 411 as a yellow crystalline solid (12.3 g, 55%). ^1H NMR (DMSO- d_6 , 400 MHz) δ 6.8 (s, 1H), 6.95 (d, 1H), 7.4 (m, 2H), 7.8 (s, 1H), 8.25 (s, 1H),
20 10.45 (s, 1H).



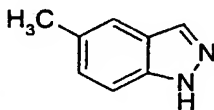
25

412

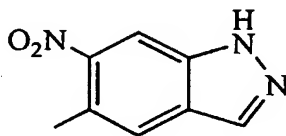
Phenol **411** (12.3 g, 55.3 mmol), potassium carbonate (38.21 g, 277 mmol), ethyl bromoacetate (6.4 mL, 57.7 mmol), and acetone (250 mL) were used as in general procedure II to afford **412** as a yellow/orange foam (15.9 g, 93%). MS (ES⁻) *m/z* 279 (M-H)⁻. The crude product was used without purification.

**413**

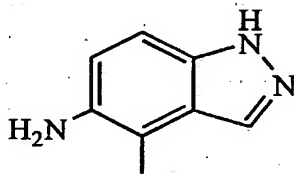
- 10 Compound **415** (0.4 g, 2.3 mmol), palladium on carbon (0.12 g, 10% w/w), and ethanol (50 mL) were used as in general procedure XII using 60 psi of hydrogen to afford **413** as a tan solid (0.35 g, crude material). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.05 (s, 3H), 4.96 (bs, 2H), 6.56 (s, 1H), 7.22 (s, 1H), 7.63 (s, 1H), 12.16 (s, 1H); MS (ES⁻) *m/z* 148 (M-H)⁻.

**414**

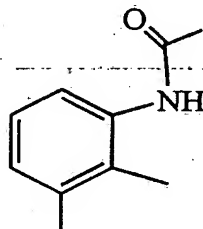
- 15 Potassium nitrate (10.13 mL, 100 mmol) in concentrated sulfuric acid (50 mL) was added dropwise to a stirred solution of concentrated sulfuric acid (50 mL) and 2,4-
20 dimethylaniline (Aldrich, 4.94 g, 40.8 mmol) at 0 °C. The reaction was stirred for 3 h. The mixture was poured into ice water (1800 mL) and extracted with ethyl acetate. The organics were separated and concentrated in vacuo to afford **414** as an orange solid (2.98 g, 44%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.02 (s, 3H), 2.3 (s, 3H), 7 (s, 1H), 7.26 (s, 1H).

**415**

Sodium nitrite (0.67 g, 9.7 mmol) in water (4 mL) was added dropwise to a stirred solution of compound **414** (1.6 g, 9.6 mmol) and glacial acetic acid (250 mL) at 0 °C. The reaction was stirred for 15 min. at 0 °C, and rt for 3 h. The reaction was stored for 9 d. The mixture was concentrated in vacuo. The concentrate was triturated with water and the resulting slurry was stirred for 1 h. The slurry was filtered and washed with water. The solid was dissolved in methylene chloride and washed with water. The organics were separated and further purified by flash chromatography using 9:1 hexanes:ethyl acetate and 1:1 hexanes:ethyl acetate to afford **415** as a red solid (0.4 g, 19%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.5 (s, 3H), 7.82 (s, 1H), 8.17 (d, 2H), 13.53 (bs, 1H).

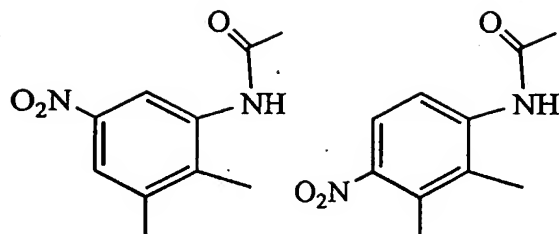
**416**

Compound **420** (1.07 g, 6 mmol), palladium on carbon (0.33 g, 10% w/w), ethanol (30 mL) and THF (20 mL) were used as in general procedure XII using 80 psi of hydrogen to afford **416** as a brown solid (0.53 g, 60%). ¹H NMR (DMSO-d₆, 300 MHz) δ 2.25 (s, 3H), 4.5 (s, 2H), 6.8 (d, 1H), 7.1 (d, 1H), 7.85 (s, 1H), 12.55 (bs, 1H). MS (ES⁻) *m/z* 148 (M-H).

**417**

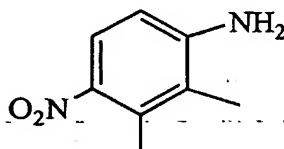
Acetic anhydride (25 mL, 265 mmol) was added to a stirred solution of 2,3-dimethylaniline (Aldrich, 31.2 g, 257 mmol) and toluene (50 mL) under nitrogen. The resulting solid was filtered and washed with hexanes and ether to afford **417** as a white solid (40.59 g, crude material). ¹H NMR (DMSO-d₆, 300 MHz) δ 2.06 (d, 6H), 2.26 (s, 3H), 7.05 (m, 2H), 7.15 (d, 1H), 9.35 (bs, 1H).

263



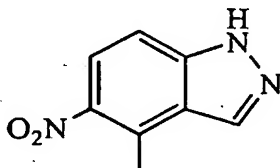
418

Potassium nitrate (6.2 g, 61 mmol) in concentrated sulfuric acid (75 mL) was added dropwise over 1 h to a cooled, stirred solution of concentrated sulfuric acid (50 mL) and compound **417** (10 g, 61 mmol) at -17 °C. The cooling bath was removed and the reaction was stirred at 0 °C for 1 h. The solution was poured into ice water (2000 mL) and stirred vigorously. The solution was extracted with methylene chloride. The organics were separated, dried over MgSO₄, and concentrated in vacuo to afford a solid. The solid was purified by flash chromatography using a gradient between 7:3 hexanes:ethyl acetate and ethyl acetate as elutant to afford **418** as a yellow solid (4.24g, 33%). MS (ES⁻) *m/z* 201 (M-H)⁻. Compound **418** was used as a mixture without purification.



419

Compound **418** (4.24 g, 20.4 mmol) was added portionwise to a stirred solution of potassium hydroxide (1.2 g, 21 mmol), water (50 mL), and ethanol (200 mL) and the mixture was refluxed for 1 h. Water (50 mL) was added to the reaction dropwise and the resulting solution was cooled to rt. A precipitate was filtered and washed with water and ether. The filtrate was extracted with ether and the organics were combined, dried over MgSO₄, and concentrated in vacuo to give **419** as a yellow solid (2.02 g, 60%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2 (s, 3H), 2.34 (s, 3H), 6.12 (bs, 2H), 6.5 (d, 1H), 7.6 (d, 1H).



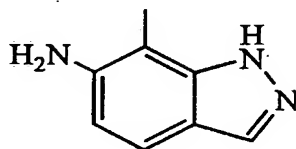
264

420

Sodium nitrite (0.42 g, 6 mmol) in water was added dropwise to a stirred solution of compound **419** (1 g, 6 mmol) and glacial acetic acid (50 mL) at 0°C and stirred for 1 h.

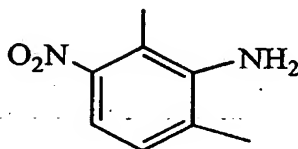
- 5 The reaction was stored for 2 d at rt. The mixture was concentrated in vacuo and the concentrate was triturated with water. The resulting solid was filtered and washed with water to afford **420** as a tan solid (2.07 g, crude material). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.8 (s, 3H), 7.5 (d, 1H), 7.95 (d, 1H), 8.45 (s, 1H), 13.6 (bs, 1H); MS (ES⁻) *m/z* 176 (M-H).

10

**421**

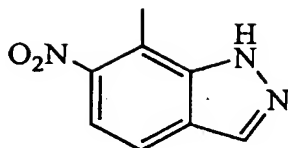
- 15 Compound **423** (2.69 g, 15.2 mmol), palladium on carbon (0.8 g, 10% w/w), ethanol (100 mL), and THF (20 mL) were used as in general procedure XII using 60 psi of hydrogen to afford **421** as a tan solid (1.43 g, 63.8%). The crude material was used without purification.

20

**422**

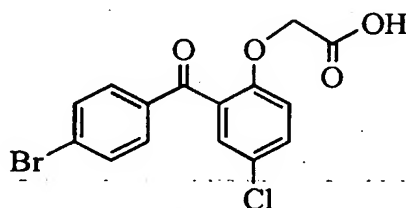
- Potassium nitrate (10.13 mL, 100 mmol) in concentrated sulfuric acid (50 mL) was added dropwise to a stirred solution of concentrated sulfuric acid (50 mL) and 2,6-dimethylaniline (Aldrich, 12.32 g, 100 mmol) at -10 °C and stirred for 1 h. The mixture was poured into ice water and extracted with ethyl acetate. The organics were separated, dried over MgSO₄, and concentrated in vacuo to afford **422** as an orange solid (5.63 g, 34%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.05 (d, 6H), 5.4 (bs, 2H), 6.9 (d, 1H), 6.96 (d, 2H). The crude material was used without purification.
- 25
- 30

265



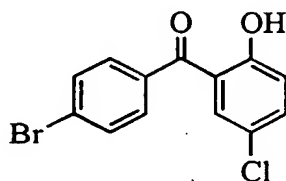
423

- 5 Sodium nitrite (2.34 g, 34 mmol) in water (10 mL) was added dropwise to a stirred solution of compound 422 (5.63 g, 34 mmol) and glacial acetic acid (500 mL) at 0°C and stirred for 15 min. The cooling bath was removed and the reaction was stored at rt for 6 d. The mixture was concentrated in vacuo and the concentrate was triturated with water. The resulting solid was filtered and recrystallized from methanol to give 423 as a red solid
- 10 (2.69 g, 45%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.73 (s, 3H), 3.15 (s, 3H), 7.64 (d, 1H), 7.9 (d, 1H), 8.24 (s, 1H), 13.85 (bs, 1H). MS (ES⁻) *m/z* 176 (M-H)⁻. The crude material was used without purification.



424

- 15 Ester 426 (16.72 g, 42 mmol), ethanol (EtOH, 200 mL), water (50 mL), and lithium hydroxide monohydrate (2.21 g, 52 mmol) were used as in general procedure III to afford
- 20 424 as an off-white solid (10.71 g, 69%). The crude material was used without purification.

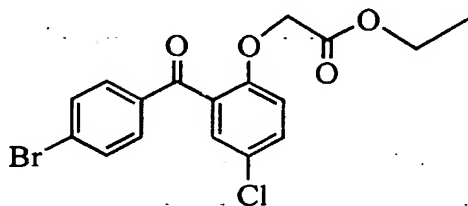


425

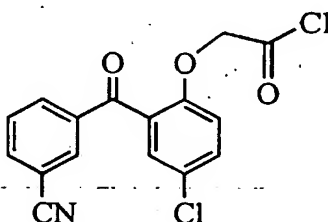
25

266

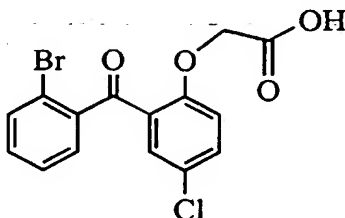
4-Bromobenzoyl chloride (8.73 g, 40 mmol), aluminum chloride (AlCl_3 , 5.3 g, 40 mmol), CH_2Cl_2 (125 mL), and 4-chloroanisole (4.87 mL, 40 mmol) were used as in general procedure I to afford **425** as a yellow solid (14.27 g, crude material).

**426**

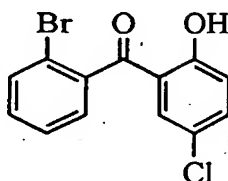
Compound **425** (14.27 g, 65 mmol), potassium carbonate (45 g, 325 mmol), ethyl bromoacetate (7.57 mL, 68 mmol), and acetone (250 mL) were used as in general procedure II to afford **426** as a tan solid (16.72 g, 65%). ^1H NMR (DMSO-d_6 , 400 MHz) δ 4.6(s, 2H), 7.07 (d, 1H), 7.4 (d, 1H), 7.54 (dd, 1H), 7.64 (m, 4H), 13.04 (bs, 1H). The crude material was used without purification.

**427**

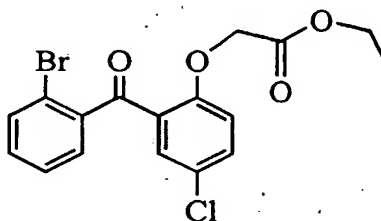
Carboxylic acid **129** (1.5 g, 4.8 mmol), methylene chloride (30 mL), and thionyl chloride (10 mL, 137 mmol) were used as in general procedure XV to afford **427** as an off-white, sticky solid (1.58 g, crude material).

**428**

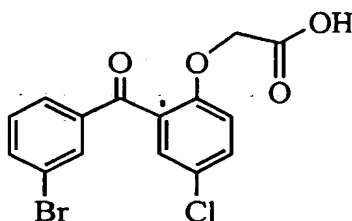
Ester **430** (17.24 g, 43 mmol), ethanol (200 mL), water (50 mL), and lithium hydroxide monohydrate (2.27 g, 54 mmol) were used as in general procedure III to afford **123** as a white solid (6.53 g, 41%).

**429**

2-Bromobenzoyl chloride (10 g, 46 mmol), aluminum chloride (AlCl_3 , 6.2 g, 46 mmol), CH_2Cl_2 (250 mL), and 4-chloroanisole (5.6 mL, 46 mmol) were used as in general procedure I to afford **429** as a tan solid (13.76 g, crude material).

**430**

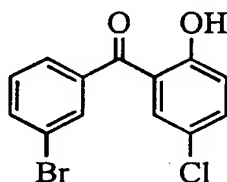
Compound **429** (13.76 g, 44 mmol), potassium carbonate (30.52 g, 221 mmol), ethyl bromoacetate (5.14 mL, 46 mmol), and acetone (250 mL) were used as in general procedure II to afford **430** as a yellow solid (17.24 g, crude material). ^1H NMR (DMSO-d_6 , 400 MHz) δ 4.5 (s, 2H), 7.15 (d, 1H), 7.4 (s, 4H), 7.48 (d, 1H), 7.58 (d, 1H), 7.65 (d, 1H), 12.95 (bs, 1H).

**431**

Ester **433** (17.24 g, 43 mmol), ethanol (EtOH, 200 mL), water (50 mL), and lithium hydroxide monohydrate (2.27 g, 54 mmol) were used as in general procedure III to afford

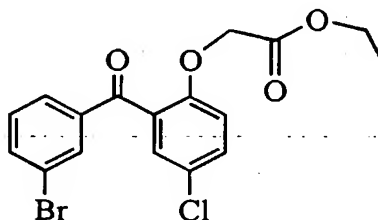
431 as a white solid (6.53 g, 41%). ¹H NMR (DMSO-d₆, 400 MHz) δ 4.65 (s, 2H), 7.08 (d, 1H), 7.42 (m, 2H), 7.54 (dd, 1H), 7.71 (d, 1H), 7.83 (dd, 2H), 13.00 (bs, 1H); MS (ES⁺) *m/z* 371 (M+H)⁺. The crude material was used without purification.

5

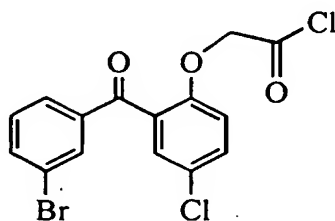
**432**

3-Bromobenzoyl chloride (24.11 g, 110 mmol), aluminum chloride (AlCl₃, 15 g, 113 mmol), CH₂Cl₂ (250 mL), and 4-chloroanisole (13.46 mL, 110 mmol) were used as in general procedure I to afford, after triturating the concentrate with hexanes and filtering, **432** as a green solid (25.57 g, 75%). The crude material was used without purification.

15

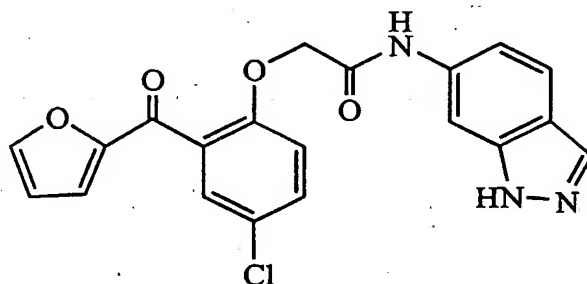
**433**

Compound **432** (9.08 g, 29 mmol), potassium carbonate (20.14 g, 146 mmol), ethyl bromoacetate (3.39 mL, 31 mmol), and acetone (200 mL) were used as in general procedure II to afford **433** as a red/brown oil (12.68 g, crude material). ¹H NMR (DMSO-d₆, 400 MHz) δ 1.12 (t, 3H), 4.06 (q, 2H), 4.75 (s, 2H), 7.11 (d, 1H), 7.44 (t, 2H), 7.54 (d, 1H), 7.69 (d, 1H), 7.83 (d, 2H); MS (ES⁺) *m/z* 398 (M+H)⁺.

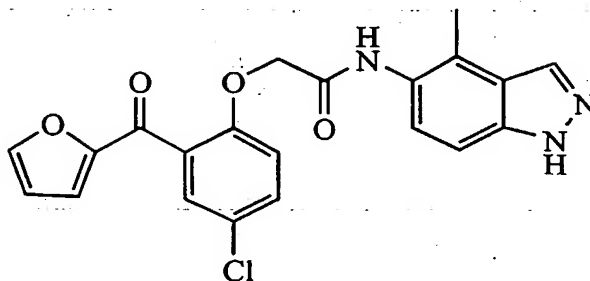


434

Carboxylic acid **431** (3 g, 8.1 mmol), methylene chloride (25 mL), and thionyl chloride (11.84 mL, 162 mmol) were used as in general procedure XV to afford **434** as a light brown oil (2.96 g, 94%). The crude material was used without purification.

Example 173**435**

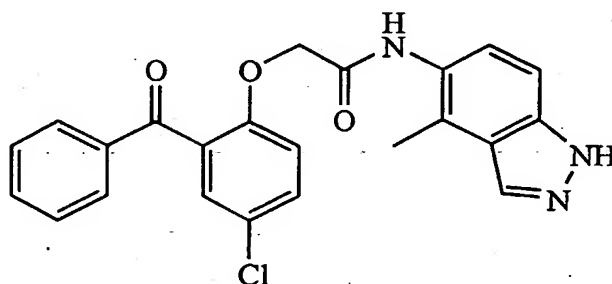
Compound **115** (0.28 g, 1 mmol), HCA (0.08 mL, 0.5 mmol), THF (50 mL total reaction volume), PPh_3 (0.26 g, 1 mmol) in THF, and 6-aminoindazole (0.13 g, 1 mmol) in THF were used as in general procedure XIII. The product was purified by flash chromatography using a gradient between 1:1 hexanes:ethyl acetate and 100% ethyl acetate to afford **435** as an orange oil (0.042 g, 11%). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 4.8 (s, 2H), 6.7 (d, 1H), 7.05 (d, 1H), 7.2 (d, 2H), 7.35 (d, 1H), 7.5 (d, 1H), 7.55 (dd, 1H), 7.65 (d, 1H), 7.94 (s, 1H), 8.07 (s, 2H), 10.06 (s, 1H), 12.89 (s, 1H).

Example 174**436**

Compound **115** (0.19g, 0.68 mmol), HOBT (0.09 g, 0.68 mmol), DMF (1 mL), **416** (0.1 g, 0.68 mmol) in DMF, EDAC (0.13 g, 0.69 mmol) in DMF (5 mL total reaction volume), and Et_3N (0.19 mL, 1.36 mmol) were used as in general procedure IV. The product was

purified by flash chromatography using 1:1 and 7:3 ethyl acetate:hexanes to afford **436** as an off-white solid (0.126 g, 11%). ^1H NMR (DMSO- d_6 , 400 MHz) δ 2.25 (s, 3H), 4.8 (s, 2H), 6.7 (s, 1H), 7.18-7.35 (m, 4H), 7.5 (s, 1H), 7.6 (d, 1H), 8.05 (dd, 2H), 9.35 (s, 1H), 13 (s, 1H).

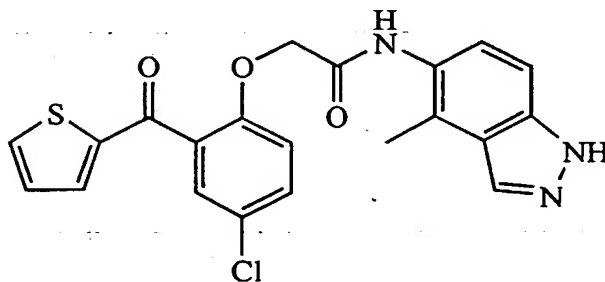
Example 175



437

Compound **416** (0.1 g, 0.68 mmol), NEt_3 (0.14 mL, 0.71 mmol), acetonitrile (5 mL total reaction volume), and acid chloride **1** (0.53 g, 1.7 mmol) in acetonitrile were used as in general procedure X. The product was purified by flash chromatography using 1:1 hexanes:ethyl acetate to afford **437** as an off-white solid (0.095 g, 33%). ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.28 (s, 3H), 4.78 (s, 2H), 7.15 (d, 1H), 7.3 (t, 2H), 7.55 (dd, 3H), 7.65 (t, 2H), 7.82 (d, 2H), 8.13 (s, 1H), 9.18 (s, 1H), 13.04 (bs, 1H); MS (ES^+) m/z 420 ($\text{M}+\text{H}^+$).

Example 176

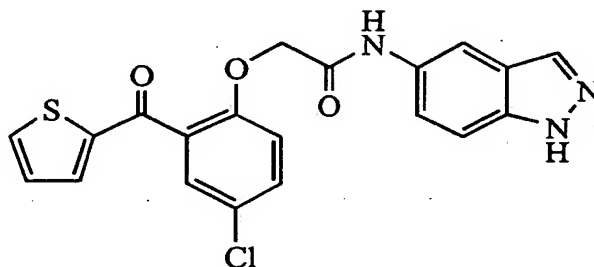


438

Compound **112** (0.20g, 0.67 mmol), HOBt (0.09 g, 0.68 mmol), DMF (2 mL), compound **416** (0.1 g, 0.68 mmol) in DMF (3 mL), EDAC (0.13 g, 0.69 mmol), and Et_3N (0.19 mL, 1.36 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 7:3 ethyl acetate:hexanes and 100% ethyl acetate to afford **438** as

an off-white solid (0.192 g, 67%). ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.3 (s, 3H), 4.85 (s, 2H), 7.2-7.35 (m, 4H), 7.55 (s, 1H), 7.65 (d, 1H), 7.7 (s, 1H), 8.15 (s, 2H), 9.38 (s, 1H), 13.05 (s, 1H); MS (ES $^-$) m/z 424 (M-H) $^-$.

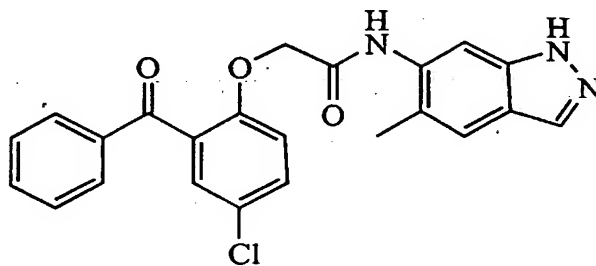
5 **Example 177**



439

Compound 112 (0.20g, 0.67 mmol), HOBt (0.09 g, 0.68 mmol), DMF (2 mL), 5-
10 aminoindazole (Aldrich, 0.09 g, 0.68 mmol) in DMF (3 mL), EDAC (0.13 g, 0.69 mmol),
and Et $_3$ N (0.19 mL, 1.36 mmol) were used as in general procedure IV. The product was
purified by flash chromatography using 1:1 ethyl acetate:hexanes as elutant and further
purified by dissolving in ethyl acetate, washing with water, drying organics over MgSO $_4$
and concentrating in vacuo to afford 439 as an off-white solid (0.071 g, 26%). ^1H NMR
15 (DMSO- d_6 , 400 MHz) δ 4.8 (s, 2H), 7.2 (d, 2H), 7.35 (d, 1H), 7.5 (d, 2H), 7.55 (d, 1H),
7.65 (s, 1H), 8 (t, 3H), 9.85 (s, 1H), 13 (s, 1H).

Example 178

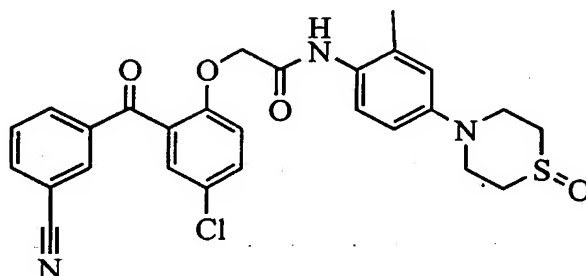


440

Compound 413 (0.1 g, 0.68 mmol), NEt $_3$ (0.19 mL, 2.6 mmol), acetonitrile (30 mL), and
acid chloride 320 (0.21 g, 0.68 mmol) in acetonitrile (10 mL) were used as in general
procedure X. The product was purified by flash chromatography using 7:3 hexanes:ethyl
25 acetate then 1:1 hexanes:ethyl acetate as elutant, and a TLC prep plate eluted with 1:1
hexanes:ethyl acetate to afford 440 as an off-white solid (0.019 g, 6.7%). ^1H NMR

(DMSO- d_6 , 300 MHz) δ 2.28 (s, 3H), 4.78 (s, 2H), 7.15 (d, 1H), 7.3 (t, 2H), 7.49 (m, 3H), 7.64 (t, 2H), 7.8 (d, 2H), 8.1 (s, 1H), 9.18 (s, 1H), 13 (bs, 1H); MS (ES⁺) m/z 420 (M+H)⁺.

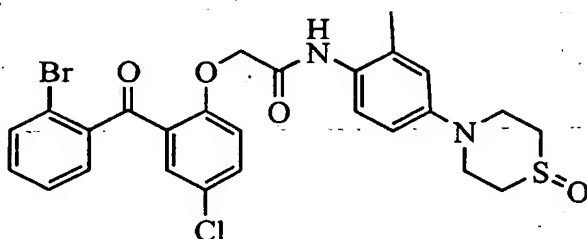
Example 179



441

Compound 399 (1.2 g, 5.4 mmol) in acetonitrile (45 mL total reaction volume), acid chloride 427 (1.22 g, 3.65 mmol) in acetonitrile, and NEt₃ (0.71 mL, 5.1 mmol) were used as in general procedure X. The product was purified by flash chromatography using 95:5 methylene chloride:methanol as elutant to afford 441 as an off-white solid (0.59 g, 31%).
¹H NMR (DMSO- d_6 , 400 MHz) δ 1.97 (s, 3H), 2.6 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.67 (s, 2H), 6.75 (d, 1H), 6.82 (s, 1H), 7.06 (d, 1H), 7.2 (d, 1H), 7.48 (s, 1H), 7.65 (t, 2H), 8.05 (bs, 2H), 8.15 (s, 1H), 8.96 (s, 1H).

Example 180

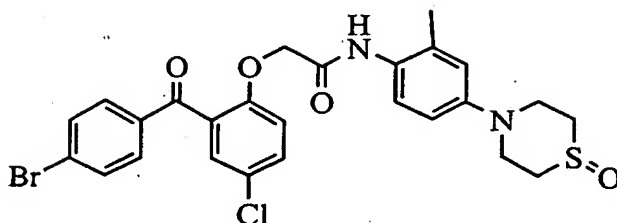


442

Compound 428 (0.443 g, 1.2 mmol), HOBT (0.16 g, 1.2 mmol), DMF, compound 399 (0.40 g, 1.8 mmol) in DMF (15 mL total reaction volume), EDAC (0.23 g, 1.2 mmol), and Et₃N (0.34 mL, 2.4 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford 442 as an off-white foam (0.154 g, 22%).
¹H NMR (DMSO- d_6 , 400 MHz) δ 2.07 (s, 3H), 2.6 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.62 (s, 2H), 6.78 (d, 1H), 6.84

(s, 1H), 7.15 (d, 1H), 7.25 (d, 1H), 7.38 (t, 1H), 7.42 (d, 2H), 7.5 (t, 1H), 7.65 (m, 2H), 8.8 (s, 1H).

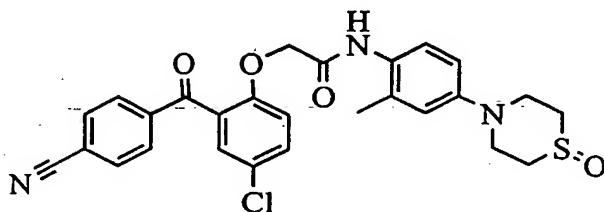
Example 181



443

Compound **424** (0.443 g, 1.2 mmol), HOBT (0.16 g, 1.2 mmol), DMF, compound **399** (0.40 g, 1.8 mmol) in DMF (15 mL total reaction volume), EDAC (0.23 g, 1.2 mmol), and Et₃N (0.34 mL, 2.4 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford **443** as a pale yellow foam (0.105 g, 15%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.06 (s, 3H), 2.75 (d, 2H), 2.95 (t, 2H), 3.6 (d, 2H), 3.8 (t, 2H), 4.77 (s, 2H), 6.88 (d, 1H), 6.92 (s, 1H), 7.15 (d, 1H), 7.3 (d, 1H), 7.55 (d, 1H), 7.72 (d, 2H), 7.78 (s, 4H), 8.97 (s, 1H); MS (ES⁺) *m/z* 574 (M-H)⁺.

Example 182

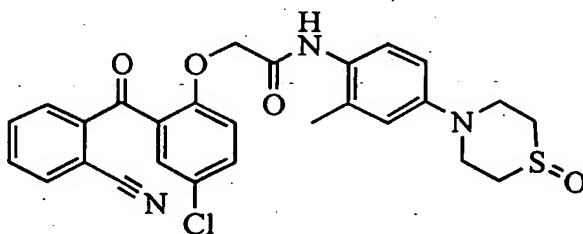


444

Copper cyanide (0.029 g, 0.33 mmol) was added to a solution of compound **443** (0.093 g, 0.16 mmol) in DMSO (5 mL) and the reaction was heated to 160°C and stirred overnight. The mixture was cooled and water was added to it. The resulting solid was filtered and washed with ethyl acetate. The filtrate was separated, dried over MgSO₄, and concentrated in vacuo. The product was purified by flash chromatography using a gradient between 9:1 hexanes:ethyl acetate and ethyl acetate as the elutant to afford **444** as

an orange foam (0.012 g, 14%). ^1H NMR (DMSO- d_6 , 400 MHz) δ 1.95 (s, 3H), 2.65 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.64 (s, 2H), 6.75 (dd, 1H), 6.82 (s, 1H), 7.02 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 7.63 (d, 2H), 7.9 (m, 4H), 8.88 (s, 1H); MS (ES $^-$) m/z 521 (M-H).

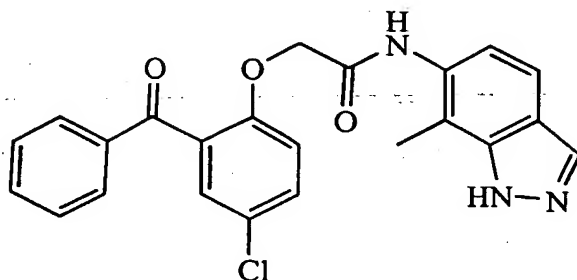
Example 183



445

Copper cyanide (0.037 g, 0.42 mmol) was added to a solution of compound 442 (0.120 g, 0.21 mmol) in DMSO (5 mL) and the reaction was heated to 160 °C and stirred overnight. The mixture was cooled and water was added to it. The resulting solid was filtered and washed with ethyl acetate. The filtrate was separated, dried over MgSO_4 , and concentrated in vacuo. The product was purified by flash chromatography using a gradient between 9:1 hexanes:ethyl acetate and ethyl acetate as the elutant to afford 445 as an orange foam (0.012 g, 11%). ^1H NMR (DMSO- d_6 , 400 MHz) δ 1.99 (s, 3H), 2.62 (d, 2H), 2.86 (t, 2H), 3.5 (d, 2H), 3.69 (t, 2H), 4.62 (s, 2H), 6.75 (d, 1H), 6.82 (s, 1H), 7.05 (d, 1H), 7.2 (d, 1H), 7.55 (d, 1H), 7.7 (m, 4H), 7.98 (d, 1H), 8.97 (s, 1H); MS (ES $^-$) m/z 521 (M-H).

Example 184

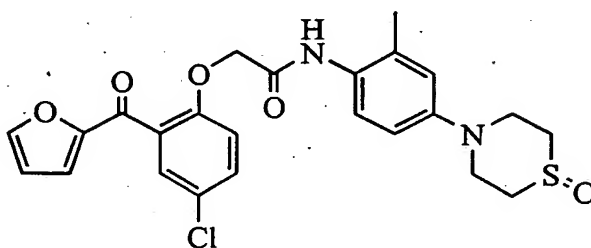


446

Carboxylic acid **105** (0.296 g, 1.2 mmol), HOBT (0.136 g, 1.02 mmol), DMF, compound **421** (0.296 g, 1.02 mmol) in DMF (10 mL total reaction volume), EDAC (0.193 g, 1.02 mmol), and Et₃N (0.284 mL, 2.04 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 1:1 ethyl acetate:hexanes as elutant.

5 The concentrate was dissolved in methylene chloride, washed with 10% potassium carbonate. The organics were separated, dried over MgSO₄, and concentrated in vacuo. The resulting solid was triturated with ethyl acetate and filtered to afford **446** as an off-white solid (0.0081 g, 2%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.2 (s, 3H), 4.74 (s, 2H), 6.95 (d, 1H), 7.22 (d, 1H), 7.45 (m, 4H), 7.6 (m, 2H), 7.75 (d, 2H), 7.98 (s, 1H), 9.25 (s, 1H) 13.05 (bs, 1H); MS (ES⁺) *m/z* 420 (M+H)⁺.

Example 185

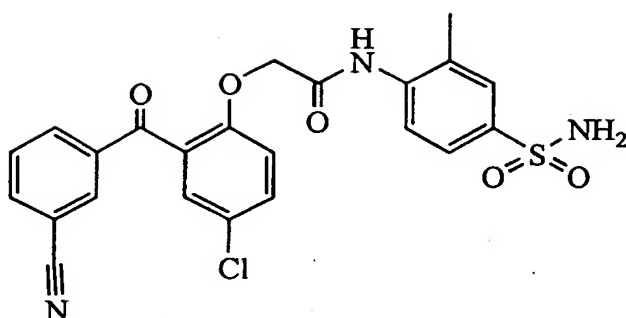


447

15 Compound **399** (0.314 g, 1.4 mmol) in acetonitrile (10 mL total reaction volume), acid chloride **408** (0.3 g, 1 mmol) in acetonitrile, and NEt₃ (0.24 mL, 1.7 mmol) were used as in general procedure X. The product was dissolved in methylene chloride and washed
20 with saturated potassium carbonate and water then purified by flash chromatography using 95:5 methylene chloride:methanol as elutant to afford **447** as an off-white foam (0.305 g, 63%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.03 (s, 3H), 2.63 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.74 (s, 2H), 6.71 (d, 1H), 6.78 (d, 1H), 6.84 (s, 1H), 7.18 (m, 2H), 7.3 (d, 1H), 7.5 (d, 1H), 7.59 (dd, 1H), 8.06 (s, 1H), 9.02 (s, 1H); MS (ES⁺) *m/z* 487 (M+H)⁺.

Example 187

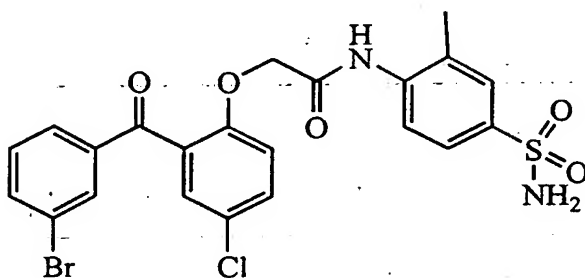
276



448

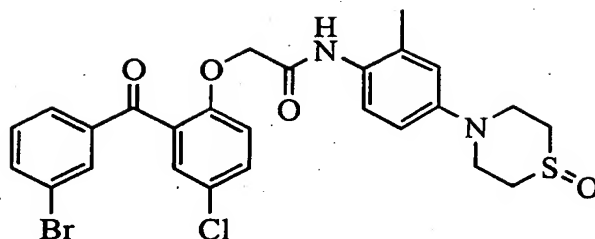
Compound 466 (0.15 g, 0.8 mmol) in acetonitrile (10 mL total reaction volume), acid
chloride 427 (0.2 g, 0.6 mmol) in acetonitrile, and NEt_3 (0.112 mL, 0.8 mmol) were used
as in general procedure X. The product was purified by flash chromatography using 95:5
methylene chloride:methanol as elutant and TLC prep plate eluted twice with 98:2
methylene chloride:methanol to afford 448 as an off-white solid (0.104 g, 36%). ^1H NMR
(DMSO- d_6 , 400 MHz) δ 2.14 (s, 3H), 4.78 (s, 2H), 7.22 (m, 3H), 7.49 (d, 1H), 7.61 (m,
10 3H), 7.68 (t, 1H), 8.06 (d, 2H), 8.17 (s, 1H), 9.39 (s, 1H); MS (ES $^-$) m/z 482 (M-H).

Example 187

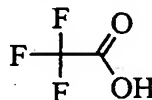
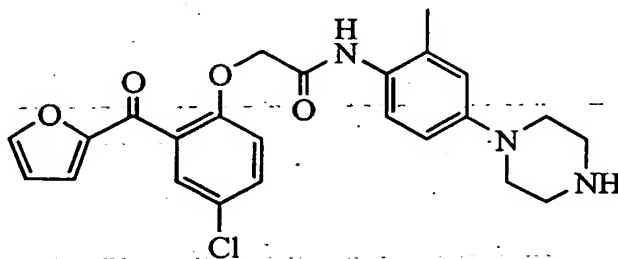


449

Compound 466 (0.141 g, 0.757 mmol), NEt_3 (0.106 mL, 0.761 mmol), acetonitrile (20 mL
total reaction volume), and acid chloride 434 (0.203 g, 0.523 mmol) were used as in
general procedure X. The product was purified by flash chromatography using 98:2
methylene chloride:methanol as elutant to afford 449 as an off-white solid (0.038 g, 14%).
 ^1H NMR (DMSO- d_6 , 400 MHz) δ 2.14 (s, 3H), 4.77 (s, 2H), 7.22 (m, 3H), 7.45 (dd, 2H),
15 7.6 (m, 4H), 7.72 (d, 1H), 7.82 (d, 1H), 7.88 (s, 1H), 9.3 (s, 1H); MS (ES $^-$) m/z 536 (M-H).

Example 188**450**

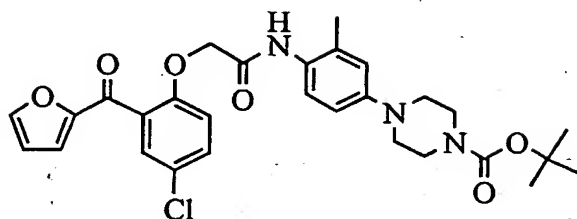
Compound 399 (1.43 g, 6.37 mmol), NEt_3 (0.888 mL, 6.37 mmol), acetonitrile (50 mL total reaction volume), and acid chloride 434 (1.68 g, 4.64 mmol) were used as in general procedure X. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford **450** as an beige solid (1.3 g, 52%). ^1H NMR (DMSO- d_6 , 400 MHz) δ 1.98 (s, 3H), 2.62 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.69 (t, 2H), 4.67 (s, 2H), 6.75 (dd, 1H), 6.82 (d, 1H), 7.08 (d, 1H), 7.2 (d, 1H), 7.42 (d, 1H), 7.46 (d, 1H), 7.62 (dd, 1H), 7.7 (d, 1H), 7.81 (d, 1H), 7.88 (s, 1H), 8.9 (s, 1H); MS (ES $^-$) m/z 574 (M-H) $^-$.

Example 189**451**

Trifluoroacetic acid (TFA, 5 mL, 65 mmol) was added to a solution of compound 452 (0.095 g, 0.17 mmol) in acetonitrile (10 mL) and stirred at rt under nitrogen overnight. Carbon tetrachloride was added to the reaction mixture and the resulting solution was concentrated in vacuo to azeotrope off the TFA. This procedure was repeated multiple times. The product was purified by flash chromatography using 1:1 hexanes:ethyl acetate as elutant to afford **451** as a red/orange solid (0.012 g, 16%). ^1H NMR (DMSO- d_6 , 400 MHz) δ 2.04 (s, 3H), 3.15 (s, 4H), 3.21 (d, 4H), 4.75 (s, 2H), 6.7 (d, 1H), 6.75 (d, 1H), 6.8

(s, 1H), 7.2 (dd, 2H), 7.3 (d, 1H), 7.5 (d, 1H), 7.58 (d, 1H), 8.06 (s, 2H), 8.19 (bs, 1H), 9.05 (s, 1H); MS (ES⁺) *m/z* 454 (M+H)⁺.

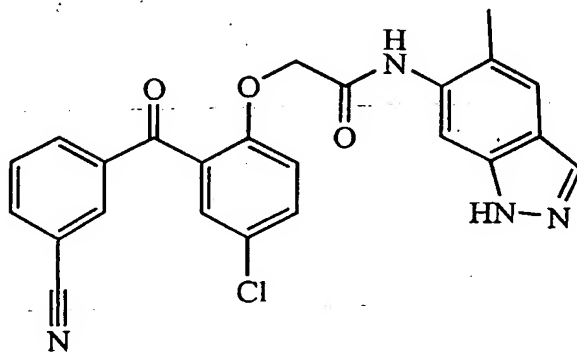
Example 190



452

Compound 367 (0.409 g, 1.4 mmol) in acetonitrile (5 mL total reaction volume), acid chloride 408 (0.3 g, 1 mmol) in acetonitrile, and NEt₃ (0.24 mL, 1.7 mmol) were used as in general procedure X. The product was purified by flash chromatography using 99:1 methylene chloride:methanol as elutant to afford 452 as a brown, viscous oil (0.202 g, 36%). ¹H NMR (DMSO-d₆, 400 MHz) δ 1.38 (s, 9H), 2.02 (s, 3H), 3.01 (d, 4H), 3.4 (d, 4H), 4.74 (s, 2H), 6.72 (d, 2H), 6.77 (s, 1H), 7.19 (t, 2H), 7.3 (d, 1H), 7.5 (d, 3H), 7.57 (dd, 1H), 8.05 (s, 1H), 9.01 (s, 1H); MS (ES⁻) *m/z* 553 (M-H)⁻.

Example 191

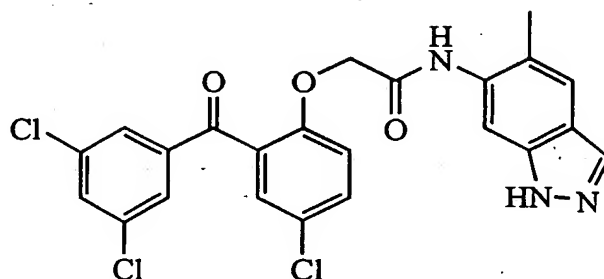


453

Compound 413 (0.072 g, 0.49 mmol) in acetonitrile (10 mL total reaction volume), acid chloride 427 (0.163 g, 0.49 mmol) in acetonitrile, and NEt₃ (0.1 mL, 0.72 mmol) were used as in general procedure X. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford 453 as an off-white solid (0.013 g,

6%). ^1H NMR (DMSO- d_6 , 400 MHz) δ 2.16 (s, 3H), 4.77 (s, 2H), 7.25 (d, 1H), 7.5 (s, 2H), 7.65 (m, 3H), 7.89 (s, 1H), 8.08 (d, 2H), 8.16 (s, 1H), 9.03 (s, 1H), 12.84 (s, 1H); MS (ES $^-$) m/z 443 (M-H).

5 **Example 192**

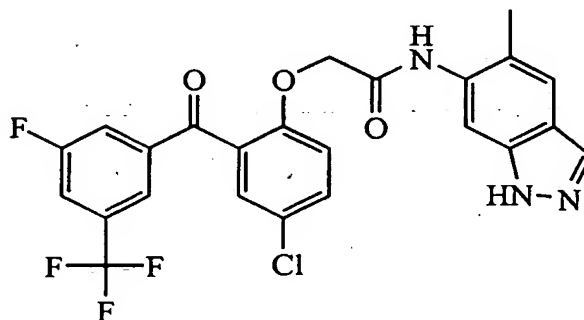


454

10 Carboxylic acid 76 (0.2 g, 0.55 mmol), methylene chloride (CH_2Cl_2 , 3 mL), DMF (4 drops), oxalyl chloride (0.13 mL, 1.49 mmol) were used as in general procedure V. The resulting acid chloride was added to a solution of the amine 413 (0.081 g, 0.55 mmol), acetone (5 mL), sodium bicarbonate (0.42 g, 5 mmol), and water (0.5 mL) as used in
15 general procedure VI. The solution was heated to 40°C for 1 h, after which time water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to afford 454 as a gray solid (0.045 g, 17%). ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.2 (s, 3H), 4.85 (s, 2H), 7.3 (d, 1H), 7.56 (s, 2H), 7.7 (d, 1H), 7.77 (s, 3H), 7.9 (s, 2H), 9.2 (s, 1H), 12.9 (s, 1H); MS (ES $^-$) m/z 486 (M-H).

20

Example 193

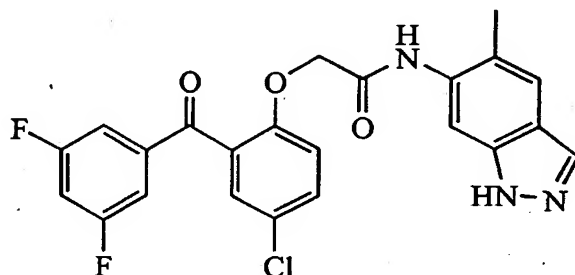


455

Carboxylic acid **71** (0.2 g, 0.53 mmol), methylene chloride (3 mL), DMF (4 drops), oxalyl chloride (0.123 mL, 1.41 mmol) were used as in general procedure V. The resulting acid chloride was then added to a solution of the amine **103** (0.078 g, 0.53 mmol), acetone (5 mL), sodium bicarbonate (0.4 g, 4.76 mmol), and water (0.5 mL) as used in general
5 procedure VI. The reaction mixture was heated to 40°C for 1 h, after which time water (25 mL) was added to the mixture and the resulting suspension was filtered. The solids were washed with ether to afford **455** as a gray solid (0.048 g, 18%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.13 (s, 3H), 4.78 (s, 2H), 7.2 (d, 1H), 7.5 (d, 2H), 7.65 (d, 2H), 7.88 (s, 3H), 7.98 (d, 1H), 9.15 (bs, 1H), 12.8 (bs, 1H); MS (ES⁺) *m/z* 504 (M-H).

10

Example 194



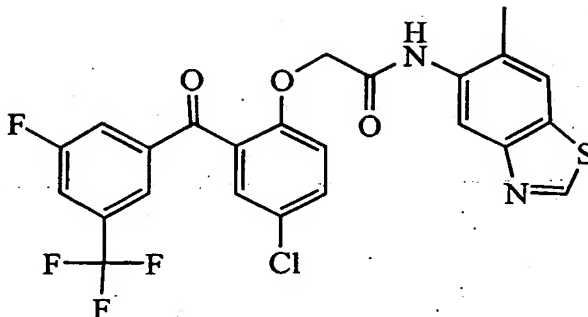
15

456

Carboxylic acid **49** (0.2 g, 0.6 mmol), methylene chloride (3 mL), DMF (4 drops), oxalyl chloride (0.16 mL, 1.8 mmol) were used as in general procedure V. The resulting acid chloride was then added to a solution of the amine **413** (0.09 g, 0.61 mmol), acetone (10 mL), sodium bicarbonate (0.453 g, 5.4 mmol), and water (0.5 mL) as used in general
20 procedure VI. The reaction mixture was heated to 40 °C for 1 h, after which time water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to give a gray solid. The product was purified by filtering through a silica gel plug eluted with 9:1 hexanes:ethyl acetate. Hexanes were added to
25 the filtrate until a solid formed. The solid was filtered to afford **456** as a white solid (0.034 g, 12%). ¹H NMR (DMSO-d₆, 300 MHz) δ 2.2 (s, 3H), 4.85 (s, 2H), 7.3 (d, 1H),

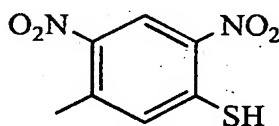
7.5 (d, 2H), 7.56 (d, 2H), 7.62(d, 1H), 7.7 (d, 1H), 7.77 (s, 1H), 7.95 (s, 1H), 9.19 (s, 1H), 12.9 (s, 1H); MS (ES⁺) m/z 454 (M-H)⁺.

5 **Example 195**



457

10 **Step A:**

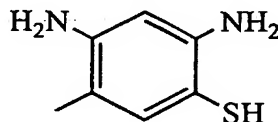


458

15 Sodium sulfide nonahydrate (3.19 g, 13.3 mmol) was added to a solution of 5-fluoro-2,4-dinitrotoluene (Maybridge, 2.47 g, 12.3 mmol) in DMF (20 mL) and the resulting mixture was stirred overnight under nitrogen. Water was added to the reaction and the solution was acidified to pH 2. The suspension was filtered and the solids were washed with 1N HCl to afford **458** as a yellow/orange solid (4.73 g, crude material). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.46 (s, 3H), 7.89 (s, 1H) 8.7 (s, 1H).

20

Step B:

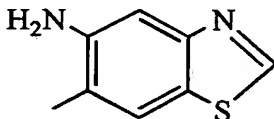


459

25

Compound 458 (2.64 g, 12.3 mmol), palladium on carbon (2 g, 10% w/w), ethanol (200 mL) and THF (100 mL) were used as in general procedure XII to afford 459 as a yellow solid (0.35 g, 18%). The crude material was used without purification.

5 **Step C:**



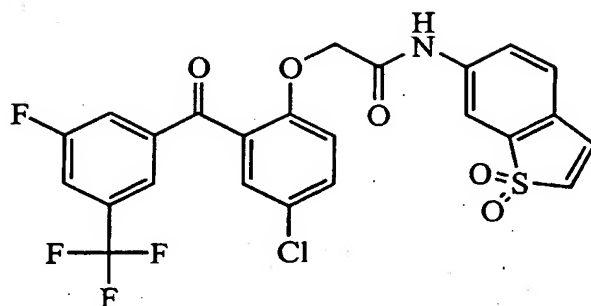
460

Formic acid (96%, 20 mL) was added to compound 459 in a round-bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand. The mixture was refluxed overnight. The mixture was poured into 2N NaOH (200 mL) and the pH was adjusted to 10. The mixture was extracted with ether, dried over MgSO₄, and concentrated in vacuo to give an oil. The product was purified by flash chromatography using a gradient between 1:1 hexanes:ethyl acetate and ethyl acetate as elutant to afford 460 as a white solid (0.03g, 8%). ¹H NMR (DMSO-d₆, 300 MHz) δ 2.2 (s, 3H), 5.09 (bs, 2H), 7.28 (s, 1H), 7.66 (s, 1H), 9.1 (s, 1H); MS (ES⁺) *m/z* 165 (M+H)⁺.

20 **Step D:**

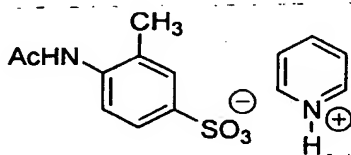
Carboxylic acid 71 (0.091 g, 0.24 mmol), methylene chloride (3 mL), DMF (4 drops), oxalyl chloride (0.057 mL, 0.65 mmol) were used as in general procedure V. The resulting acid chloride was then added to a solution of the amine 460 (0.03 g, 0.18 mmol), acetone (5 mL), sodium bicarbonate (0.18 g, 2.1 mmol), and water (0.5 mL) as used in general procedure VI. The mixture was filtered and the solids were washed with water, ether, and ethyl acetate to afford 457 as an off-white solid (0.064 g, 67%). ¹H NMR (DMSO-d₆, 400 MHz) δ 2.18 (s, 3H), 4.79 (s, 2H), 7.25 (d, 1H), 7.54 (d, 1H), 7.65 (dd, 1H), 7.88 (d, 2H), 7.95 (s, 1H), 7.98 (d, 1H), 8.06 (s, 1H), 9.27 (s, 1H), 9.38 (bs, 1H); MS (ES⁻) *m/z* 521 (M-H)⁻.

30 **Example 196**

**461**

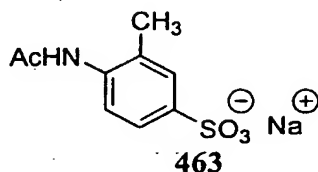
Carboxylic acid **71** (0.091 g, 0.24 mmol), methylene chloride (3 mL), DMF (4 drops),
5 oxalyl chloride (0.057 mL, 0.65 mmol) were used as in general procedure V and added to
a solution of 6-amino-1,1-dioxobenzo(b)thiophene (Maybridge, 0.044 g, 0.24 mmol),
acetone (10 mL), sodium bicarbonate (0.184 g, 2.2 mmol), and water (1 mL) as used in
general procedure VI. The product was purified by filtering through a silica pad eluted
with methylene chloride. The organics were washed with saturated sodium bicarbonate,
10 dried over MgSO_4 , and concentrated in vacuo. The product was further purified by flash
chromatography using 9:1 methylene chloride:methanol as elutant to afford **461** as a
yellow solid (0.013 g, 10%). ^1H NMR (DMSO-d_6 , 400 MHz) δ 4.75 (s, 2H), 7.2 (d, 1H),
7.25 (d, 1H), 7.5 (d, 1H), 7.54-7.58 (m, 2H), 7.59-7.64 (m, 2H), 7.85 (d, 2H), 7.9 (d, 1H),
8 (s, 1H), 10.4 (s, 1H); MS (ES^-) m/z 538 (M-H^-).

15

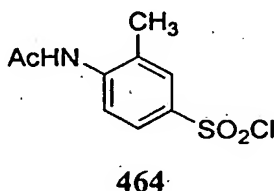
**462**

Into a round-bottom flask were placed 2-aminotoluene-5-sulfonic acid (50.0 g, 267 mmol),
and pyridine (300 mL). Acetic anhydride (38 mL, 403 mmol) was added dropwise from an
20 addition funnel and the resulting mixture was allowed to stir for 2 h at rt. The solvents
were removed under reduced pressure, to leave a brown solid. Several portions of ethyl
alcohol were added to the solid and subsequently removed under reduced pressure, to
afford a brown solid which was filtered and washed with several additional portions of
ethyl alcohol and dried under vacuum (67.03 g, 81%) ^1H NMR (DMSO-d_6 ,) δ 2.08 (s,

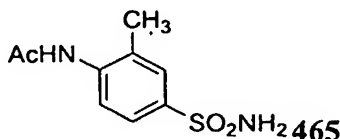
3H), 2.22 (s, 3H), 7.39 (s, 2H), 7.45 (s, 1H), 8.02 (t, J= 6 Hz, 2H), 8.53 (t, J= 6Hz, 1H), 8.92 (d, J= 6Hz, 2H), 9.31 (s, 1H).



Compound 462 (67.03 g, 217 mmol) was added to a round-bottom flask containing 1N NaOH (225 mL) and the resulting mixture was allowed to stir at rt for 3 h. The mixture was concentrated under reduced pressure, to afford a brown solid. Several portions of ethyl alcohol were added and subsequently removed under reduced pressure. The remaining solid was filtered, washed with a final portion of ethyl alcohol and dried under vacuum (42.34 g, 77%). ¹H NMR (DMSO-d₆, 300 MHz) δ 2.08 (s, 3H), 2.22 (s, 3H), 7.39 (s, 2H), 7.45 (s, 1H), 9.31 (s, 1H).

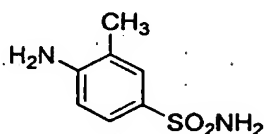


Sulfonic acid salt 463 (42.34 g, 169 mmol) and DMF (300 mL) were added to a flask that was equipped with a stir bar and nitrogen on demand and was cooled to 0 °C. Thionyl chloride (30 mL, 411 mmol) was added dropwise from an addition funnel at a rate such that the temperature of the reaction mixture did not exceed 10 °C. When the addition was complete, the mixture was allowed to warm to rt and stir for an additional 2 1/2 h, after which time it was poured into a beaker containing crushed ice. The resulting solid was collected by filtration, washed with several portions of water and dried under vacuum (25.63 g, 61%). ¹H NMR (DMSO, d₆, 400 MHz) δ 2.02 (s, 3H), 2.15 (s, 3H), 7.33 (s, 2H), 7.38 (s, 1H), 9.27 (s, 1H).



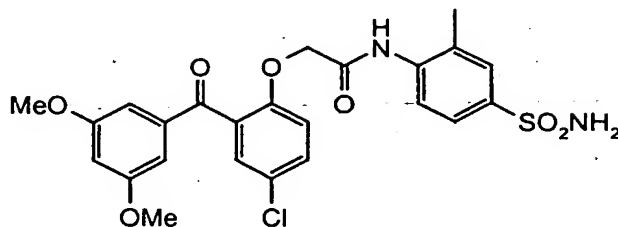
Into a round-bottom flask, equipped with a stir bar and nitrogen on demand, were placed sodium acetate (19.82 g, 241.6 mmol) and ethyl alcohol (200 mL) and the mixture was

cooled to 0 °C. Ammonia gas was bubbled through the sodium acetate solution for 5 min, then sulfonyl chloride 464 (25.63 g, 103 mmol) was added as a solid and in one portion. The resulting mixture was allowed to stir at 0 °C for 30 min, and was then allowed to warm to rt and stir for an additional 18 h. The mixture was then diluted with water and was poured into a separatory funnel containing water and ethyl acetate. The organic layer was collected, washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to provide 465 as a yellow solid (8.4 g, 36%), which was used without further purification.



466

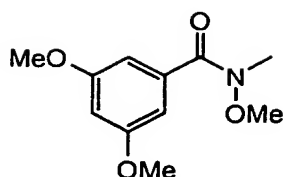
A round-bottom flask was equipped with a stir bar, a reflux condenser and nitrogen on demand. Into the flask were placed sulfonamide 465 (8.4 g, 36.80 mmol), ethyl alcohol (200 mL) and 2N hydrochloric acid (128 mL). The resulting mixture was allowed to heat to reflux overnight, after which time it was allowed to cool to RT and was neutralized with saturated, aqueous sodium bicarbonate. It was then poured into a separatory funnel containing water and ethyl acetate, the organic layer was collected, washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to afford a tan solid (6.35 g, 93%), which was used without further purification. ¹H NMR (DMSO-d₆, 400 MHz) δ 2.06 (s, 3H), 5.54 (s, 2H), 6.58 (d, J= 12 Hz, 1H), 6.82 (s, 2H), 7.30 (d, J= 12 Hz, 1H), 7.33 (s, 1H).

Example 197:

467

Step A:

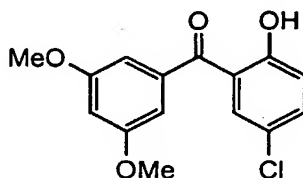
286



468

The title compound was prepared according to General Procedure VII from 3,5-dimethoxybenzoyl chloride (2.00 g, 10.0 mmol). The reaction gave 468 as a colorless oil (2.143 g, 95%): ^1H NMR (CDCl_3 , 400 MHz) δ 6.75 (d, 2 H), 6.49 (t, 1 H), 3.76 (s, 6 H), 3.55 (s, 3 H), 3.29 (s, 3 H).

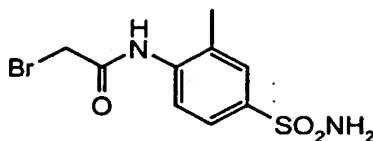
Step B:



469

A solution of 2-bromo-4-chlorophenol (0.830 g, 4.0 mmol) in 20 mL of THF was cooled to -78°C in a dry ice/acetone bath. *n*-Butyllithium (5.5 mL of a 1.6 M solution in hexanes, 8.8 mmol) was added dropwise over 5 min, and the resulting mixture was stirred at -78°C for 1 h. A solution of 468 (0.901 g, 4.0 mmol) in 5 mL of THF was added dropwise over 4 min, and the resulting mixture was stirred at -78°C for 1.25 h, then at room temperature for 14 h. The reaction mixture was poured into 50 mL of water and extracted with two 50-mL portions of EtOAc. The combined organic layers were then dried over MgSO_4 , filtered and concentrated *in vacuo* to give 1.193 g of a brown oil. Purification by flash chromatography using 10% EtOAc/hexanes as an eluant followed by crystallization from hot ether gave 469 as yellow crystals (0.234 g, 20%): ^1H NMR (CDCl_3 , 300 MHz) δ 11.83 (s, 1 H), 7.62 (d, 1 H), 7.45 (dd, 1 H), 7.03 (d, 1 H), 6.76 (d, 2 H), 6.68 (t, 1 H), 3.84 (s, 6 H).

Step C:



470

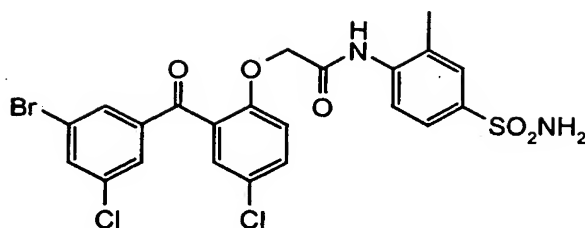
A solution of 466 (5.0 g, 26.85 mol) and pyridine (2.4 mL, 29.53 mmol) in 150 mL of
5 chloroform was cooled to 0 °C in an ice bath. Bromoacetyl bromide (2.6 mL, 29.53
mmol) was added dropwise over 20 min, and the resulting mixture was allowed to slowly
warm to room temperature as it was stirred for 18 h. The reaction mixture was then
poured into 150 mL of water and extracted with two 100-mL portions of CH₂Cl₂. Both the
organic and aqueous layers were filtered to yield a beige solid. This solid was suspended
10 in 40 mL of 1 N HCl and stirred several minutes. The solid was then filtered and rinsed
with CH₂Cl₂, MeOH, and hexanes to yield 470 (5.705 g, 69%): ¹H NMR (CDCl₃, 400
MHz) δ 9.84 (s, 1H), 7.66-7.56 (m, 3 H), 7.23 (br s, 2 H), 4.09 (s, 2 H), 2.24 (s, 3 H).

Step D:

15 A mixture of 469 (0.144 g, 0.49 mmol), 470 (0.162 g, 0.53 mmol), and potassium
carbonate (0.339 g, 2.45 mmol) in 5 mL of acetone was warmed to reflux for 6 h, then
stirred at room temperature overnight. The reaction mixture went dry overnight, so
another 5 mL of acetone was added, and the resulting mixture was heated to reflux for 8 h,
then stirred at room temperature for 22 h. The reaction mixture was poured into 30 mL of
20 water and extracted with two 30-mL portions of EtOAc. The combined organic layers
were filtered to remove solid, washed with brine, dried over MgSO₄, filtered, and
concentrated *in vacuo* to give 0.195 g of a yellow solid. Purification by suspension in hot
ether followed by filtration gave 467 (0.094 g, 37%): MS (AP+) *m/z* 518.9 (M+H); ¹H
NMR (DMSO-d₆, 400 MHz) δ 9.15 (s, 1H), 7.63-7.60 (m, 3 H), 7.56 (dd, 1 H), 7.39 (d, 1
25 H), 7.22 (s, 2H), 7.18 (d, 1 H), 6.82 (d, 2 H), 6.71 (t, 1 H), 4.76 (s, 2 H), 3.69 (s, 6 H), 2.12
(s, 3 H).

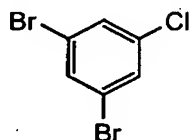
Example 198:

288



471

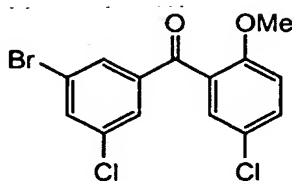
Step A:



472

A solution of 1,3,5-tribromobenzene (9.44 g, 30 mmol) in 120 mL of ether was cooled to -78°C in a dry ice/acetone bath. *n*-Butyllithium (13.2 mL of 2.5 M solution in hexanes, 33 mmol) was added dropwise over 10 min. The resulting mixture was stirred at -78°C for an additional 10 min, then hexachloroethane (7.15 g, 30.2 mmol) was added in small portions over 3 min. The reaction mixture was then stirred for 15 min at -78°C , followed by 3.2 h at rt. The mixture was partitioned between 100 mL of water and 100 mL of EtOAc. The aqueous layer was separated and extracted with an additional 100 mL of EtOAc. The combined organic layers were then dried over MgSO_4 , filtered, and concentrated *in vacuo* to give 472 as a pale brown solid (7.72 g, 95%): ^1H NMR (CDCl_3 , 300 MHz) δ 7.57 (t, 1 H), 7.47 (d, 2 H).

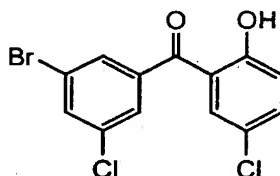
Step B:



473

A solution of **472** (7.62 g, 28.2 mmol) in 100 mL of ether was cooled to -78°C in a dry ice/acetone bath. *n*-Butyllithium (12.6 mL of 2.5 M solution in hexanes, 31.5 mmol) was added dropwise over 30 min. The resulting mixture was stirred at -78°C for an additional 13 min, then **183** (6.57 g, 28.6 mmol) was added in small portions over 23 min. The reaction mixture was then stirred for 22 h as the bath was allowed to warm to room temperature. The mixture was poured into 100 mL water and extracted with two 100-mL portions of EtOAc. The combined organic layers were then dried over MgSO_4 , filtered, and concentrated *in vacuo* to give 9.46 g of a beige solid. Recrystallization from hot MeOH gave **473** (6.45 g, 64%): MS (AP-)-*m/z* 358 (M-H); ^1H NMR (CDCl_3 , 300 MHz) δ 7.76 (t, 1 H), 7.70 (t, 1 H), 7.65 (t, 1 H), 7.47 (dd, 1 H), 7.36 (d, 1 H), 6.95 (d, 1 H), 3.72 (s, 3 H).

Step C:

**474**

15

The title compound was prepared according to General Procedure IX from **473** (0.338 g, 0.94 mmol). The reaction gave **474** (0.325 g, 100%): ^1H NMR (CDCl_3 , 400 MHz) δ 11.54 (s, 1 H), 7.72 (t, 1 H), 7.62 (d, 1 H), 7.52 (d, 1 H), 7.46 (dd, 1 H), 7.41 (d, 1 H), 7.02 (d, 1 H).

20

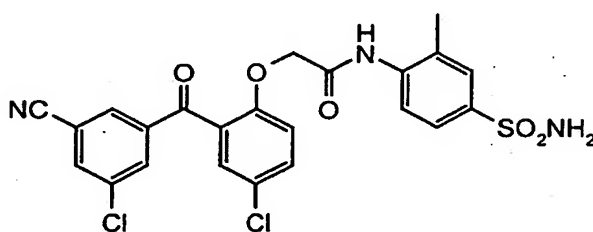
Step D:

A mixture of **474** (0.173 g, 0.50 mmol), **470** (0.154 g, 0.50 mmol), and potassium carbonate (0.346 g, 2.5 mmol) in 10 mL of acetone was warmed to reflux for 15 h and stirred at room temperature another 4 h. The reaction mixture was then poured into 35 mL of water and extracted with two 35-mL portions of EtOAc. The aqueous layer was then filtered and extracted with another 20 mL of EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated *in vacuo* to give 0.230 g

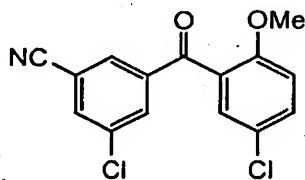
25

of a yellow oil. Purification by flash chromatography using 0.5-1% MeOH/CH₂Cl₂ gave **471** (0.048 g, 17%): MS (AP+) *m/z* 573 (M+H); ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.36 (s, 1 H), 7.97 (t, 1 H), 7.79 (s, 1 H), 7.71 (s, 1 H), 7.68-7.47 (m, 4 H), 7.45 (d, 1 H), 7.21 (s, 2 H), 7.20-7.18 (d, 1 H), 4.77 (s, 2 H), 2.13 (s, 3 H).

5

Example 199:**475**

Step A:

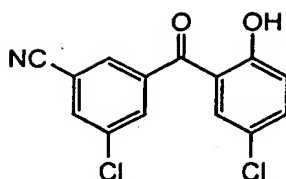
**476**

A solution of **473** (0.299 g, 0.83 mmol), sodium cyanide (0.086 g, 1.76 mmol), copper (I) iodide (0.028 g, 0.15 mmol), and tetrakis-(triphenylphosphine)-palladium (0.113 g, 0.10 mmol) in 8 mL of acetonitrile was heated to reflux for 40 min. The reaction mixture was then diluted with 50 mL of EtOAc and filtered through Celite. The resulting solution was washed with 25 mL of water, dried over MgSO₄, filtered and concentrated *in vacuo* to give 0.375 g of an orange gum. Purification by flash chromatography using 5% EtOAc/hexane as the eluant gave **476** (0.171 g, 56%): ¹H NMR (CDCl₃, 400 MHz) δ 7.93 (t, 1 H), 7.82 (t, 1 H), 7.76 (t, 1 H), 7.47 (dd, 1 H), 7.37 (d, 1 H), 6.93 (d, 1 H), 3.67 (s, 3 H).

20

Step B:

291



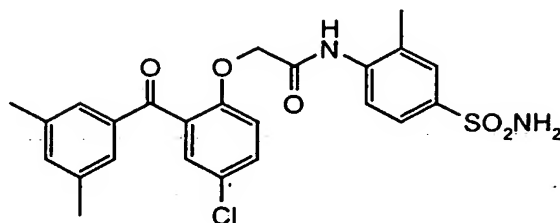
477

The title compound was prepared according to General Procedure IX from 476 (0.165 g, 0.54 mmol). The reaction gave 477 (0.174 g, 100%): ^1H NMR (CDCl_3 , 400 MHz) δ 11.43 (s, 1 H), 7.84-7.82 (m, 2 H), 7.78 (t, 1 H), 7.49 (dd, 1 H), 7.34 (d, 1 H), 7.05 (d, 1 H).

Step C:

A mixture of 477 (0.157 g, 0.54 mmol), 470 (0.165 g, 0.54 mmol), and potassium carbonate (0.373 g, 2.7 mmol) in 10 mL of acetone was warmed to reflux for 17.5 h. The reaction mixture was then poured into 35 mL of water and extracted with two 35-mL portions of EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated *in vacuo* to give 0.276 g of a yellow oil. Purification by flash chromatography using 0.5-1% MeOH/ CH_2Cl_2 gave 475 (0.033 g, 12%): MS (AP-) m/z 517 (M-H); ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 9.42 (s, 1 H), 8.26 (s, 1 H), 8.11 (s, 1 H), 8.03 (t, 1 H), 7.63 (dd, 1 H), 7.60-7.53 (m, 3 H), 7.49 (d, 1 H), 7.22 (s, 2 H), 7.19 (d, 1 H), 4.77 (s, 2 H), 2.14 (s, 3 H).

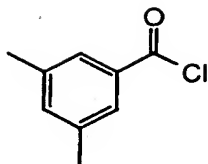
Example 200:



478

292

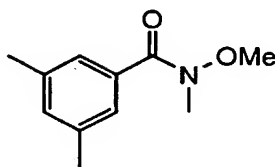
Step A:



479

- 5 The title compound was prepared according to General Procedure V from 3,5-dimethylbenzoic acid (1.50 g, 10.0 mmol). The reaction work-up gave 479 (2.214 g), which was used immediately without purification.

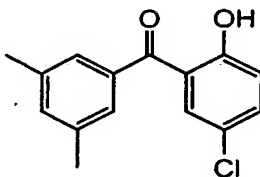
Step B:



480

10 The title compound was prepared according to General Procedure VII from 479 (2.214 g). The reaction workup gave 480 as a yellow oil (2.073 g, 100%): ¹H NMR (CDCl₃, 300 MHz) δ 7.26 (s, 2 H), 7.07 (s, 1 H), 3.57 (s, 3 H), 3.33 (s, 3 H), 2.33 (s, 6 H).

Step C:

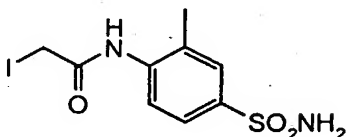


481

15

A solution of 2-bromo-4-chlorophenol (0.844 g, 4.07 mmol) in THF (20 mL) was cooled to -78°C in a dry ice/acetone bath. *n*-Butyllithium (5.6 mL of 1.6 M solution in hexanes, 8.95 mmol) was added dropwise over 6 min, and the resulting mixture was stirred at -78°C for 1 h. A solution of **480** (0.786 g, 4.07 mmol) in 5 mL of THF was added dropwise over 6 min, and the resulting mixture was stirred at -78°C for 1.25 h and at room temperature for 14 h. The reaction mixture was then poured into 50 mL of water and extracted with two 50-mL portions of EtOAc. The combined organic layers were then dried over MgSO_4 , filtered and concentrated *in vacuo* to give 1.014 g of a brown solid. Purification by flash chromatography using 5% EtOAc/hexanes as an eluant followed by crystallization from hot ether gave **481** as yellow crystals (0.296 g, 28%): ^1H NMR (CDCl_3 , 300 MHz) δ 11.94 (s, 1 H), 7.57 (d, 1 H), 7.44 (dd, 1 H), 7.25 (s, 3 H), 7.03 (d, 1 H), 2.40 (s, 6 H).

Step D:

**482**

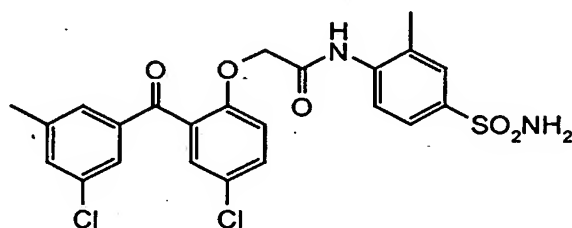
A mixture of **470** (1.27 g, 3.53 mmol) and sodium iodide (1.61 g, 10.7 mmol) in 10 mL of acetone was stirred at room temperature for 20.5 h. The reaction mixture was then diluted with 60 mL of water and 60 mL of CH_2Cl_2 and stirred for another 20 min. Filtration of the mixture then gave **482** as a beige solid (1.197 g, 96%): ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 9.81 (s, 1 H), 7.65-7.61 (m, 3 H), 7.26 (s, 2 H), 3.90 (s, 2 H), 2.28 (s, 3 H).

Step E:

A mixture of **481** (0.130 g, 0.5 mmol), **482** (0.195 g, 0.55 mmol), and potassium carbonate (0.156 g, 1.13 mmol) in 5 mL of acetone was warmed to reflux for 8 h, then stirred at room temperature an additional 12 h. The reaction mixture was then partitioned between 30 mL of water and 30 mL of EtOAc. The aqueous layer was separated and extracted

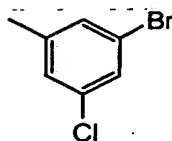
with two 30-mL portions of CH_2Cl_2 . All layers were filtered to give 0.172 g of an off-white solid. This solid was suspended in 200 mL of hot acetone and filtered again to give 0.116 g of a yellow solid. The combined organic layers were dried over MgSO_4 , filtered, and concentrated *in vacuo* to give 0.117 g of a second yellow solid. The two yellow solids
5 were combined and purified by flash chromatography using 0.5-1% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ to give 478 as a white solid (0.108 g, 44%): MS (AP+) m/z 487 (M+H); ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 9.08 (s, 1 H), 7.63-7.54 (m, 4 H), 7.36 (s, 3 H), 7.22-7.18 (m, 4 H), 4.75 (s, 2 H), 2.22 (s, 6 H), 2.10 (s, 3 H).

10 **Example 201:**



483

Step A:

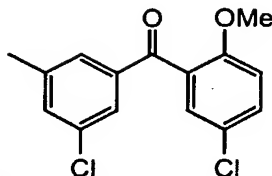


484

A solution of 3,5-dibromotoluene (1.25 g, 5.0 mmol) in 25 mL of ether was cooled to -78°C in a dry ice/acetone bath. *n*-Butyllithium (2.2 mL of 2.5 M solution in hexanes; 5.5 mmol) was added dropwise over 3 min. The resulting mixture was stirred at -78°C for an additional 11 min, then hexachloroethane (1.18 g, 5.0 mmol) was added in small portions
20 over 4 min. The reaction mixture was then stirred for 14 min at -78°C , followed by 17 h at room temperature. The reaction mixture was poured into 50 mL of water and extracted with two 50-mL portions of EtOAc. The combined organic layers were dried over MgSO_4 , filtered, and concentrated *in vacuo* to give 484 as a light brown solid (0.885 g,

86%): ^1H NMR (CDCl_3 , 300 MHz) δ 7.32 (s, 1 H), 7.22 (s, 1 H), 7.10 (s, 1 H), 2.31 (s, 3 H).

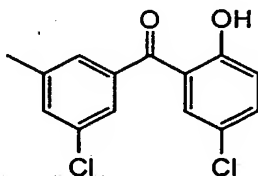
Step B:



485

A solution of 484 (0.875 g, 4.26 mmol) in 24 mL of ether was cooled to -78°C in a dry ice/acetone bath. *n*-Butyllithium (2.1 mL of 2.5 M solution in hexanes, 5.25 mmol) was added dropwise over 5 min. The resulting mixture was stirred at -78°C for an additional 15 min, then 183 (0.978 g, 4.26 mmol) was added in small portions over 6 min. The reaction mixture was then stirred for 26 h as the bath was allowed to warm to room temperature. The reaction mixture was poured into 25 mL water and extracted with 50 mL of CH_2Cl_2 . The organic layer was then dried over MgSO_4 , filtered, and concentrated *in vacuo* to give 1.224 g of a brown solid. Recrystallization from hot ether gave 485 (0.536 g, 43%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.48 (s, 1 H), 7.45 (s, 1 H), 7.40 (dd, 1 H), 7.33 (d, 1 H), 7.28 (d, 1 H), 6.90 (d, 1 H), 3.68 (s, 3 H), 2.34 (s, 3 H).

Step C:

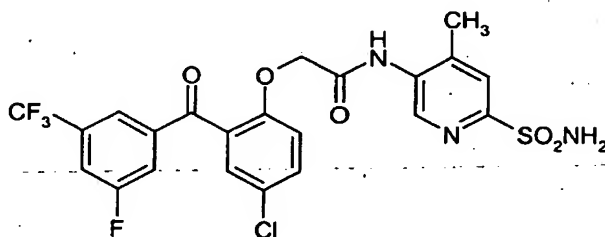
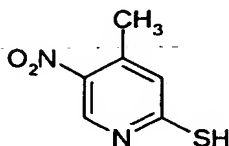


486

The title compound was prepared according to General Procedure IX from 485 (0.295 g, 1.0 mmol). The reaction gave 486 (0.285 g, 100%): ^1H NMR (CDCl_3 , 400 MHz) δ 11.71 (s, 1 H), 7.46 (d, 1 H), 7.43 (dd, 1 H), 7.39 (s, 1 H), 7.38 (s, 1 H), 7.29 (s, 1 H), 7.00 (d, 1 H), 2.40 (s, 3 H).

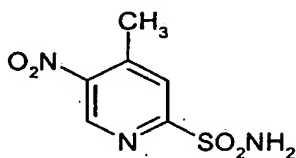
Step D:

A mixture of **486** (0.141 g, 0.5 mmol), **482** (0.195 g, 0.55 mmol), and potassium carbonate (0.138 g, 1.0 mmol) in 10 mL of acetone was warmed to reflux for 8 h, then stirred at room temperature an additional 8 h. The reaction mixture was poured into 30 mL of water and extracted with 30 mL of EtOAc and 30 mL of CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo* to give 0.238 g of crude material. Purification by flash chromatography using 0.5-2% MeOH/CH₂Cl₂ to give **483** as a white solid (0.111 g, 44%): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.23 (br s, 1 H), 7.62-7.54 (m, 4 H), 7.51 (s, 2 H), 7.49 (s, 1 H), 7.42 (d, 1 H), 7.21 (br s, 2 H), 7.19 (d, 1 H), 4.76 (s, 2 H), 2.27 (s, 3 H), 2.12 (s, 3 H).

Example 202:**487****Step A:****488**

To a heat-dried, 3-necked, round bottom flask equipped with a nitrogen inlet and reflux condenser was added 2-chloro-4-methyl-5-nitropyridine (Aldrich Chemical Co., 4.12 g,

23.9 mmol), thiourea (1.82 g, 23.9 mmol), and ethanol (40 ml). The mixture was warmed to reflux whereupon components dissolved, and the solution stirred for 3 h at reflux. A yellow precipitate was observed after 2 h. A solution of potassium hydroxide (2.01 g, 35.9 mmol) in water (8 mL) was added and the mixture was heated for an additional 1 h. The reaction mixture was allowed to cool to rt, and was diluted with 1M sodium hydroxide (150 mL). This mixture was extracted with methylene chloride (75 mL), and the pH of the aqueous layer adjusted from 12 to 7 with glacial acetic acid. The resulting solid was filtered and dried in vacuo to yield 488 (2.36 g, 58%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 8.47 (s, 1H), 7.25 (s, 1H), 2.39 (s, 3H).

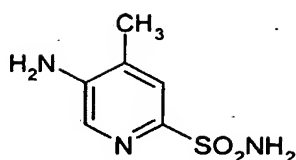
Step B:**489**

488 (850 mg, 5 mmol) was suspended in 1N hydrochloric acid (13 ml) and cooled to 0 °C.

Chlorine gas was bubbled through the suspension for 30 min, at a rate that allowed the reaction to remain near 0 °C. The reaction mix was stirred for 15 min further at 0 °C after gas introduction was stopped. Chloroform (30 ml) was added to the mixture and stirred at 0 °C until the solids dissolved. The layers were partitioned, the aqueous layer extracted with chloroform (10 mL), and the organic layers were combined, placed in a 100 ml round bottom flask and cooled in an ice/water bath. Ammonia liquid (~5 mL) was added to the solution via a cold finger trap cooled to -78 °C (CO₂/acetone). A precipitate formed and the mixture was allowed to warm to 0 °C and for 5 min, followed by 1 h at rt. The mixture was then heated to 45 °C and concentrated in vacuo to provide a yellow solid which was washed with ether and dried to give 489 (856 mg, 79%) as a tan solid. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 9.25 (s, 1H), 8.13 (s, 1H), 2.69 (s, 3H); MS (AP-): *m/z* 217 (M⁺).

Step C:

298



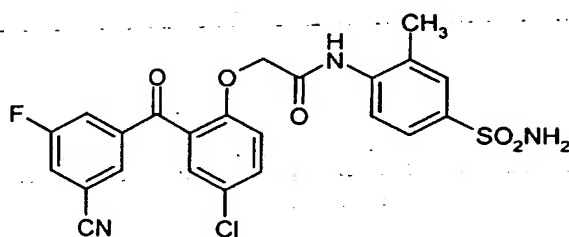
490

489 (2.36 g, 10.88 mmol) was treated according to General Procedure XII to give 490 (2.05 g, >99%), which was used without further purification.

5

StepD:

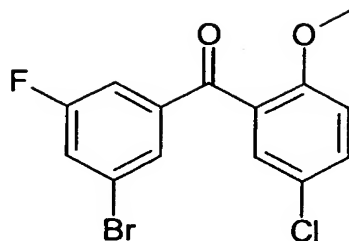
Acid 71 (200 mg, 0.53 mmol) was treated according to general procedure V. The product obtained was then allowed to react with 490 (0.53 mmol) according to general procedure VI. The resulting product was purified by silica gel chromatography (5% MeOH/CH₂Cl₂) followed by recrystallization from acetonitrile/water, to give 487 (27 mg, 9%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.7 (s, 1H), 8.61 (s, 1H), 7.97 (d, *J* = 8.4, 1H), 7.85 (m, 2H), 7.76 (s, 1H), 7.63 (dd, *J* = 9, 2.8, 1H), 7.51 (d, *J* = 2.7, 1H), 7.34 (s, 1H), 7.21 (d, *J* = 9.2, 1H), 4.80 (s, 2H), 2.17 (s, 3H); MS (ES⁺): *m/z* 546 (M⁺).

15 **Example 203**

491

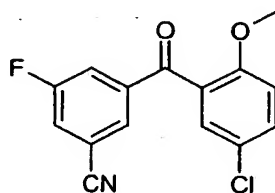
Step A:

299



492

Into a two-neck flask equipped with a nitrogen inlet was placed 3,5-dibromofluorobenzene (1.12 g, 4.4 mmol) and anhydrous ether (8 mL). This solution was cooled to -78°C ($\text{CO}_2/\text{acetone}$) and *n*-butyllithium (2.5M in hexanes, 1.92 mL, 4.8 mmol) was added dropwise. The resulting solution was stirred at -78°C for 10 min, after which time a solution of *N*-methyl-*N*-methoxy-2-methoxy-5-chlorobenzamide (1 g, 4.37 mmol) in ether (40 mL) was added dropwise. The cooling bath was removed and the reaction was allowed to warm to rt, stir for an additional for 1 h, followed by the addition of 1M H_3PO_4 (50 mL). The mixture was stirred for 30 min, and the layers were separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The product was then triturated with methanol to give **492** (0.63 mg, 42%) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 7.72 (s, 1H), 7.53 – 7.39 (m, 4H), 6.99 (d, $J = 8.9$, 1H), 3.76 (s, 3H).

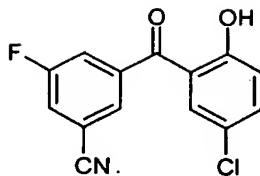
15 **Step B:**

493

492 (1.3 g, 3.8 mmol) was treated according to General Procedure XV to give **493** (1.09 g, >99%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.83 (s, 1H), 7.78 (d, $J = 8.7$, 1H), 7.60 – 7.53 (m, 2H), 7.44 (d, $J = 2.6$, 1H), 7.00 (d, $J = 8.8$, 1H), 3.75 (s, 3H); MS(EI $^{+}$): m/z 289 (M^{+}).

300

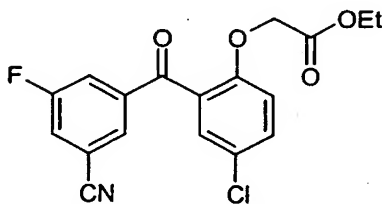
Step C:



494

- 5 493 was treated according to the procedure used for the synthesis of compound 4 to give 494 (1.09 g, >99%). ^1H NMR (CDCl_3 , 300 MHz) δ 11.51 (s, 1H), 7.79 (s, 1H), 7.67 (d, J = 7.8, 2H), 7.57 (dd, J = 9.0, 2.4, 1H), 7.44 (d, J = 2.4, 1H), 7.13 (d, J = 9.0, 1H); MS(ES $^-$): m/z 274 (M-H) $^-$.

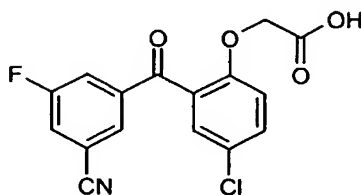
10 Step D:



495

- 494 was treated according to General Procedure II. The product was purified by silica gel chromatography (20% ethyl acetate/hexanes) to afford 495 (1.27 g, 89%) as a clear oil. ^1H NMR (CDCl_3 , 400 MHz) δ 7.90 (s, 1H), 7.80-7.78 (m, 1H), 7.50 - 7.42 (m, 3H), 6.76 (d, J = 8.6, 1H), 4.49 (s, 2H), 4.18 (q, J = 14.2, 7.1, 2H), 1.21 (t, J = 3.5, 3H).

Step E:



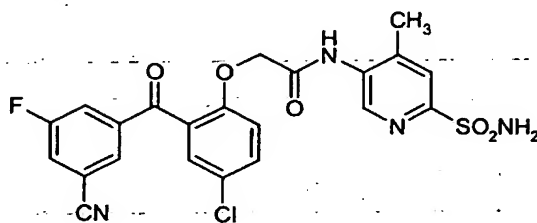
301

496

495 was treated according to General Procedure III to give 496 (1.0 g, 85%) as a white solid which was used without further purification. ¹H NMR (DMSO-*d*₆, 400MHz) δ 8.09 (d, *J* = 7.9, 1H), 8.00 (s 1H), 7.90 (d, *J* = 8.8, 1H), 7.55 (dd, *J* = 8.9, 2.5, 1H), 7.43 (d, *J* = 2.6, 1H), 7.03 (d, *J* = 9.0 2H); MS(ES-): *m/z* 332 (M-H).

Step F:

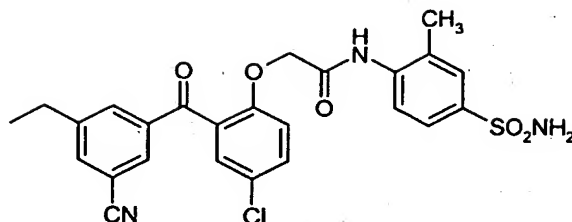
496 was used according to General Procedure V, and was further allowed to react with compound 466 according to General Procedure VI, to afford 491 (290 mg, 58%) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.43 (s, 1H), 8.1 (d, *J* = 8.2, 1H), 8.02 (s, 1H), 7.88 (d, *J* = 9.0, 1H), 7.64 – 7.48 (m, 5H), 7.22 – 7.17 (m, 3H), 4.77 (s, 2H), 2.14 (s, 3H); MS(ES-): *m/z* 500 (M-H). Anal. Calcd for C₂₃H₁₇N₃O₅ClFS: C, 55.04; H, 3.41; N, 8.37. Found: C, 55.07; H, 3.56; N, 8.35.

Example 204:

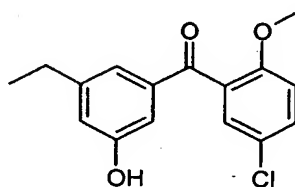
497

496 was treated according to general procedure V, and was then further allowed to react with 490 according to general procedure VI. The product was purified by silica gel chromatography (5% methanol/methylene chloride), followed and by washing with ethyl acetate/hexanes to afford 497 (48 mg, 19%). ¹H NMR (DMSO-*d*₆, 400MHz) δ 9.73 (s, 1H), 8.64 (s, 1H), 8.10 (d, *J* = 8.1, 1H), 8.02 (s, 1H), 7.88 (d, *J* = 8.8, 1H), 7.76 (s, 1H), 7.62 (dd, *J* = 8.9, 2.7, 1H), 7.49 (d, *J* = 2.5, 1H), 7.35 (s, 2H), 4.81 (s, 2H), 2.20 (s, 3H). MS(ES-): *m/z* 501 (M-H). Anal. Calcd for C₂₂H₁₆N₄O₅ClFS: C, 52.54; H, 3.21; N, 11.14. Found: C, 52.30; H, 3.34; N, 10.96.

302

Example 205:

498

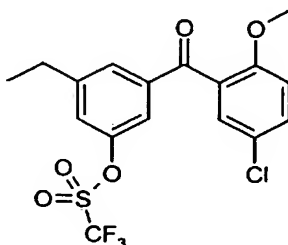
5 Step A:

499

2-bromo-4-ethylphenol (prepared according to the procedure of Sargent et al. in *J. Chem. Soc. Perkin Trans. 1*, 1984, 1621), and *N*-methyl-*N*-methoxy-2-methoxy-5-

10 chlorobenzamide were treated according to the procedures outlined by Selnick et al. in *Tetrahedron Lett.* 1993, 34, 2043-2046 to give 499 (185 mg, 11%). ¹H NMR (CDCl₃, 400MHz) δ 7.37 (dd, *J* = 8.7, 2.5, 1H), 7.32 – 7.22 (m, 1H), 7.16 (s, 1H), 7.03 (s, 1H), 6.98 – 6.84 (m, 2H), 5.16 (bs, 1H), 3.69 (s, 3H), 2.59 (q, *J* = 15.2, 7.5, 2H), 1.18 (t, *J* = 7.6, 3H).

15

Step B:

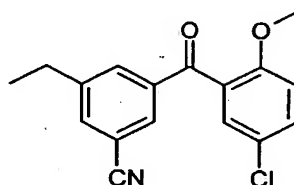
303

500

499 (185 mg, 0.64 mmol) was dissolved in DMF (2 mL) and treated with sodium hydride (31 mg 60% dispersion in oil, 0.8 mmol) and the resulting mixture was stirred for 30 min until bubbling ceased. N-phenyltriflimide (286 mg, 0.8 mmol) was added in one portion.

- 5 The mixture was stirred for 3 h, then partitioned between ether and water (50 mL each). The organic layer was dried (MgSO_4), filtered, and concentrated in vacuo to give 500 (256 mg, 95%) which was used without purification. MS(ES⁺): m/z 423 ($\text{M}+\text{H}^+$).

Step C:



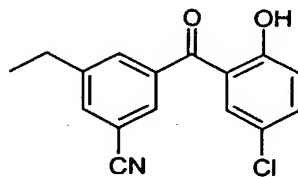
10

501

500 (256 mg, 0.61 mmol) was treated as described in General Procedure XV to give a crude product which was purified by silica gel chromatography (20% ethyl acetate/hexanes) to give 501 (158 mg, 87%). ^1H NMR (CDCl_3 , 400MHz) δ 7.85 (s, 1H), 7.74 (s, 1H), 7.63 (s, 1H), 7.44 (dd, $J = 8.9, 2.6$, 1H), 7.33 (d, $J = 2.7$, 1H), 6.91 (d, $J = 8.8$, 1H), 3.66 (s, 3H), 2.71 (q, $J = 15.2, 7.5$, 2H), 1.24 (t, $J = 7.6$, 3H).

15

Step D:



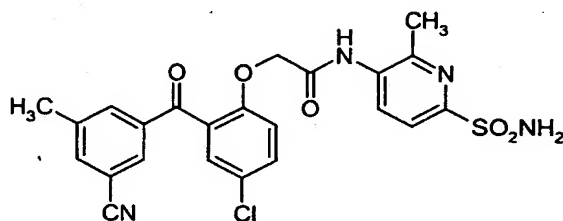
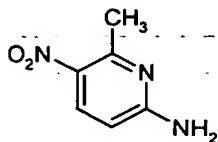
20

502

501 (158 mg, 0.53 mmol) was treated according to the procedure for the synthesis of compound 4 to give 502 (152 mg, >99%) as a yellow solid, which used without further purification. MS(ES⁻): m/z 284 ($\text{M}-\text{H}$).

Step E:

502 (152 mg, 0.53 mmol) and 470 were treated according to the procedure for the synthesis of 467 to give a crude product which was triturated with 10% methanol/ether to give 498 (100 mg, 37%). ¹H NMR (DMSO-*d*₆, 300MHz) δ 9.42 (s, 1H), 8.03 – 7.99 (m, 2H), 7.69-7.61 (m, 4H), 7.54 (d, *J* = 2.6, 1H), 4.84 (s, 2H), 2.72 (q, *J* = 15.1, 7.6, 2H), 2.20 (s, 3H), 1.19 (t, *J* = 7.5, 3H); MS(ES⁻): *m/z* 284 (M-H)⁺.

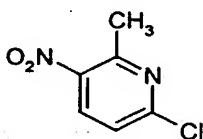
Example 206:**503****Step A:****504**

15 Concentrated sulfuric acid (200 mL) was cooled to 5 °C and 6-methyl-2-pyridinamine (50g, 0.46 mol, Aldrich Chemical Co.) was added over 20 min. while the reaction temperature was maintained below 50 °C. Fuming nitric acid (30 mL) was then added slowly over 30-40 min. and the resulting mixture was allowed to warm to rt and stand for approximately 1 h. The reaction was then heated to 55 °C for 1 h, then poured carefully
20 into a mixture of 5N sodium hydroxide (1L) and ice. The final pH was adjusted to 10 with 5N and then 1N sodium hydroxide and the product precipitated as a mixture of the 6-methyl- 4 and 5-nitro-2-pyridinamines in 75% yield. A pure sample of 504 was provided by sublimation. GCMS (EI⁺) 153 *m/z*. ¹H NMR (DMSO-*d*₆) δ 8.2 (d, 1H, Ar), 7.9

305

(bs, 2H, NH₂), 6.6 (d, 1H, Ar), 2.4 (s, 3H, CH₃). The structure was confirmed by a heteronuclear multiple bond coherence experiment (HMBC). A proton on the 6-methyl group exhibited a three bond coupling with the 5-carbon atom bearing the nitro group.

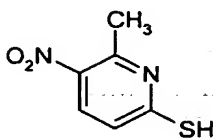
5 Step B:



505

A mixture of 504 and 6-methyl-4-nitro-2-pyridinamines (0.5g, 3.3 mmol) was stirred with carbon tetrachloride (15 mL). Trimethylsilyl chloride in dichloromethane (1M, 10 mL, 10
10 mmol) was added and the reaction heated in a 70 °C oil bath for 30 min. Trimethylsilyl chloride (0.5 mL, 4 mmol) was added the reaction was heated another 30 min. t-Butyl nitrite (4 mL, 30 mmol, 10 eq.) was added and the reaction was heated to reflux overnight. The reaction was filtered and the solvents removed in vacuo. 505 was isolated by chromatography on a 4 X 15 cm column of silica gel eluted with hexane/ethyl acetate
15 (6:1, 1 L). GCMS (CI⁺) 173 m+1/z. ¹H NMR (CDCl₃) δ 8.2 (d, 1H, Ar), 7.3 (d, 1H, Ar), 2.8 (s, 3H, CH₃). The structure was confirmed by a heteronuclear multiple bond coherence experiment (HMBC). A proton on the 6-methyl group exhibited a three bond coupling with the 5-carbon atom bearing the nitro group.

20 Step C:

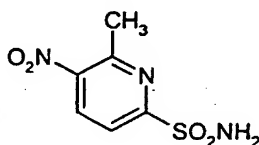


506

505 (0.4 g, 2.4 mmol) was dissolved in ethanol (30 mL). Thiourea (0.2 g, 2.6 mmol, 1.1 eq.) was added and the reaction refluxed for 7 h. Potassium hydroxide (0.2 g, 3.6 mol, 1.5
25 eq.) dissolved in water (1 mL) was added to the reaction and heating continued for 1 h.

The solution was diluted with 1N sodium hydroxide (25 mL). The aqueous phase was extracted with dichloromethane (25 mL, 3X). The pH was adjusted to 4 with concentrated HCl and **506** precipitated. A 30 % yield was obtained. LCMS (APCI⁺) 171 m+1/z. ¹H NMR (DMSO-*d*₆) δ 7.9 (d, 1H, Ar), 7.1 (d, 1H, Ar), 2.7 (s, 3H, CH₃).

Step D:

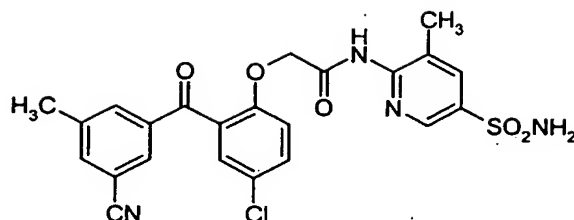
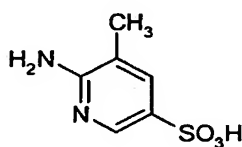


507

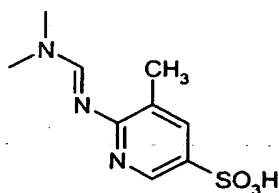
506 (0.115g, 0.67 mmol) was stirred in 1N HCl (5 mL) and chilled to 5 °C. Chlorine gas was passed through the mixture for 30 min. then the reaction was stirred for an additional 15 min. The product was extracted with dichloromethane (5 mL, 2X). The organic fractions were combined and chilled to 0 °C. Ammonia was dripped into the solution for 15 min. by condensing ammonia gas with a -78 °C cold finger. The reaction was allowed to warm to rt and stir overnight. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate (15 mL) and washed with NaHCO₃ solution (15 mL). The solution was dried with MgSO₄, filtered and the solvent removed in vacuo to give **507** in 40% yield suitable for further use. GCMS (CI⁺) 218 m+1/z. ¹H NMR (DMSO-*d*₆) δ 8.6 (d, 1H, Ar), 7.9 (d, 1H, Ar), 7.7 (bs, 2H, NH₂), 2.8 (s, 3H, CH₃).

Step E:

Reduction of the 5-nitro group of **507** (0.06 g, 0.27 mmol) was accomplished by catalytic reduction in ethanol (10 mL) with 10%Pd/C (0.011 g). The reaction was carried out overnight. The catalysis was removed by filtration and the amino compound was coupled with the acid chloride **589** generated by general procedure V, by the method outlined in general procedure VI to give **503** LCMS (ES⁺) 499 m+1/z. ¹H NMR (DMSO-*d*₆) δ 9.6 (br s, 1H, NH), 8.0 (d, 1H, Ar), 7.94 (s, 1H, Ar), 7.89 (s, 1H, Ar), 7.87 (s, 1H, Ar), 7.7 (d, 1H, Ar), 7.6 (dd, 1H, Ar), 7.45 (d, 1H, Ar), 7.32 (bs, 2H, NH₂), 7.2 (d, 1H, Ar), 4.8 (s, 2H, CH₂), 2.35 (s, 3H, CH₃), 2.33 (s, 3H, CH₃).

Example 207:**508****5 Step A:****509**

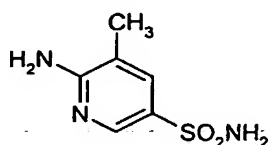
3-Methyl-2-pyridinamine (1 mL, 1 mmol, Aldrich Chemical Co.) was combined with 20% fuming sulfuric acid (2 mL) at rt. The reaction was heated to 160 °C for 20 h. The reaction was allowed to cool to rt and ice, ~10 mL, was added. The product precipitated and was collected by filtration. A 50 % yield of **509** was obtained. LCMS (ES⁺) 189 m+1/z. ¹H NMR (DMSO-*d*₆) δ 13(br s, 1H, SO₃H), 7.88(s, 3H, 1-Ar, 2H, NH₂), 7.87 (s, 1H, Ar), 2.14 (s, 3H, CH₃).

Step B:**510**

509 (0.9g, 4.8 mmol) was mixed with DMF (30 mL). Thionyl chloride (0.5 mL, 6.8 mmol, 1.4 eq.) was added and reaction stirred at rt. Solution was achieved briefly. A new precipitate formed. The reaction was stirred 30-40 min and filtered. The product was

washed with hexane and was suitable for further use. A 77% yield of **510** was obtained. LCMS (ES⁺) 244 m+1/z. ¹H NMR (DMSO-*d*₆) δ 8.4 (s, 1H, formyl-H), 7.9 (s, 2H, Ar), 3.4 (s, 3H, CH₃), 3.3 (s, 3H, CH₃), 2.35 (s, 3H, CH₃).

5 **Step C:**



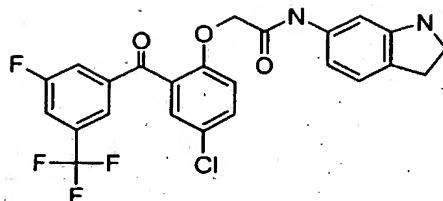
511

510 (1.0 g, 4.1 mmol) and PCl₅ (0.85 g, 4.1 mmol) were combined and heated in a 130 °C oil bath for 1.5 h. The resultant POCl₃ was removed under high vacuum. Concentrated ammonium hydroxide (25 mL) was carefully added at rt. The reaction was heated to reflux for 3 to 4 h and was then allowed to stand at rt for 60 h. The product was collected by filtration. A 45% yield of **511** was obtained. LCMS (ES⁺) 188 m+1/z. ¹H NMR (DMSO-*d*₆) δ 8.12 (s, 1H, Ar), 7.5 (s, 1H, Ar), 7.0 (s, 2H, NH₂), 6.45 (s, 1H, Ar), 2.0 (s, 3H, CH₃).

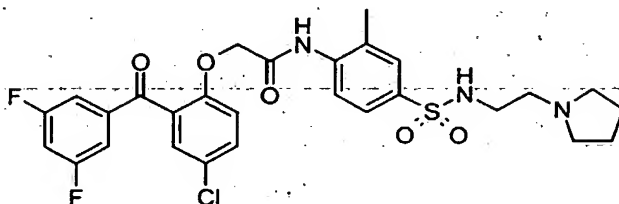
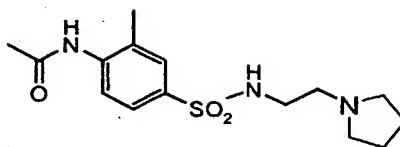
Step D:

15 **511** (0.07g, 0.37 mmol) was mixed with THF (5 mL) and (TMS)₂BSA (0.090 mL, 2 eq.). The reaction was refluxed for 45 min. The solution was cooled to rt and the acid chloride of acid (1eq.) **589**, prepared by general procedure V, was added. The reaction was stirred for 2 h at rt. The solvent was removed in vacuo. Partial purification of the product was accomplished by chromatography on a 4 X 6 cm column of silica gel eluted with
20 chloroform/ methanol (96:4) followed by chromatography on a 4 X 6 cm column of silica gel eluted with chloroform/ methanol (95:5). Final purification was accomplished by HPLC on a Waters Symmetry C18 column, 1.9 X 15 cm, eluted with MeOH/H₂O (3:2) at 8 mL/min. A 10% yield of **508** was obtained. LCMS (APCI⁺) 499 m+1/z. ¹H NMR (DMSO-*d*₆) δ 10.2 (br s, 1H, NH), 8.56 (s, 1H, Ar), 7.98 (s, 1H, Ar), 7.91 (s, 1H, Ar), 7.87 (s, 2H, Ar), 7.60 (dd, 1H, Ar), 7.47 (s, 2H, NH₂), 7.44 (s, 1H, NH₂), 7.12 (d, 1H, Ar), 4.8 (s, 2H, CH₂), 2.32 (s, 3H, CH₃), 2.10 (s, 3H, CH₃).

309

Example 208:**512**

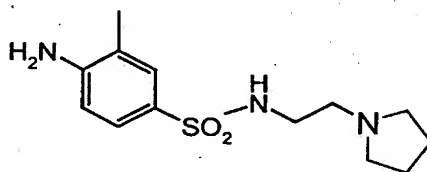
Carboxylic acid **71** (0.258 g, 0.68 mmol), oxalyl chloride (0.8 mL of 2.0 M solution in dichloromethane, 0.92 mmol), DMF (8 drops), and dichloromethane (5 mL), were used to prepare the acid chloride according to general procedure V. The acid chloride was then dissolved in acetone and added dropwise to 6-aminoindoline dihydrochloride (Aldrich, 0.140 g, 0.68 mmol), acetone (10 mL), sodium bicarbonate (0.501 g, 6 mmol), and water (1 mL) as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered, washed with water and diethyl ether, then air dried. The solids were then purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **512** (0.06 g, 18%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.92 (t, 2H), 3.94 (t, 2H), 4.93 (m, 3H), 6.21 (dd, 1H), 6.84 (d, 1H), 7.19 (d, 1H), 7.32 (m, 1H), 7.51 (d, 1H), 7.58 (dd, 1H), 8 (m, 3H); LC-MS (ES⁺) *m/z* 493 (M+H)⁺, LC-MS (ES⁻) *m/z* 491 (M-H)⁻.

Example 209:**513****Step A:**

310

514

A mixture of **464** (1.10 g, 4.4 mmol), 1-(2-aminoethyl)pyrrolidine (0.84 mL, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in methylene chloride (50 mL) was stirred rt for 6 d. The reaction mixture was then diluted with 50 mL of CH₂Cl₂ and extracted with two 50-
5 mL portions of water. The organic layer was dried over MgSO₄ and filtered to give 1.021 g of a brown oil. Purification by flash chromatography (elution with 3-5% MeOH/CH₂Cl₂) gave **514** as a yellow oil (0.776 g, 54%): MS (ES+) *m/z* 326 (M+H); ¹H NMR (CDCl₃, 400 MHz) δ 8.19-8.17 (m, 1 H), 7.70-7.68 (m, 2 H), 7.19 (br s, 1 H), 2.98 (t, 2 H), 2.52 (t, 2 H), 2.37-2.34 (m, 4 H), 2.32 (s, 3 H), 2.25 (s, 3 H), 1.73-1.70 (m, 4 H).

Step B:**515**

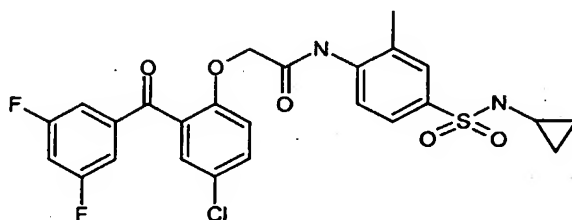
A mixture of **514** (0.765 g, 2.35 mmol) and 1.5 M HCl (5 mL) in 20 mL of ethanol was heated to 80 °C for 18 h. The reaction mixture was then poured into 50 mL of saturated
15 NaHCO₃ (aq) and extracted with two 30-mL portions of CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo* to give **515** (0.564 g, 81%): MS (ES+) *m/z* 284 (M+H); ¹H NMR (CDCl₃, 400 MHz) δ 7.54-7.50 (m, 2 H), 6.68 (d, 1 H), 4.07 (br s, 2 H), 2.98-2.95 (m, 2 H), 2.54-2.52 (m, 2 H), 2.39-2.32 (m, 4 H), 2.18 (s, 3 H), 1.75-1.68 (m, 4 H).

Step C:

Acid **49** was converted to the acid chloride using the general procedure V. Aniline **515** (0.07 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL) was
25 added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to afford **513** as an off-white solid (0.015 g, 8.7%). ¹H NMR (DMSO-

d_6 , 300 MHz) δ 1.65 (m, 4H), 2.2 (s, 3H), 2.85 (t, 2H), 3.35 (m, 6H), 4.83 (s, 2H), 7.22 (d, 1H), 7.43-7.72 (m, 8H), 9.48 (s, 1H); MS (ES⁺) m/z 592 (M+H)⁺.

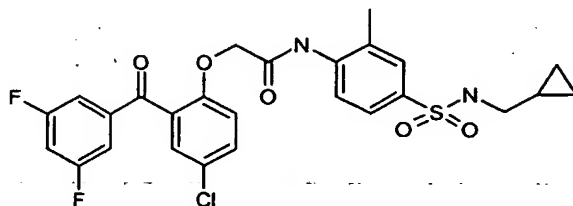
Example 210:



516

Acid 49 was converted to the acid chloride using the general procedure V. Aniline 315 (0.066 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solid was dissolved in CH₂Cl₂ then chromatographed by TLC prep plate eluted with 9:1 CH₂Cl₂:MeOH to afford **516** as an off-white solid (0.074 g, 48%). ¹H NMR (DMSO- d_6 , 400 MHz) δ 0.4 (m, 2H), 0.42 (m, 2H), 2 (m, 1H), 2.2 (s, 3H), 4.8 (s, 2H), 7.18 (d, 1H), 7.38 (m, 2H), 7.41 (d, 1H), 7.46-7.61 (m, 4H), 7.69 (d, 1H), 7.76 (d, 1H), 9.38 (s, 1H); MS (ES⁺) m/z 535 (M+H)⁺, MS (ES⁻) m/z 533 (M-H)⁻.

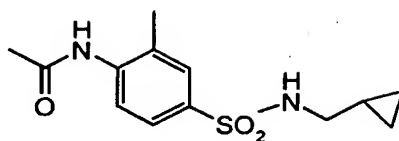
Example 211:



517

Step A:

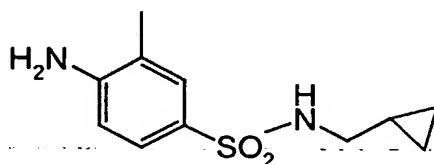
312



518

A mixture of **464** (1.10 g, 4.4 mmol), cyclopropanemethylamine (Aldrich, 0.57 mL, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in 50 mL of methylene chloride was stirred at rt for 7 d. The reaction mixture was then filtered, washed with 50 mL of CH₂Cl₂ and 50 mL of water. The organic layer was washed with an additional 50 mL of water, brine, dried over MgSO₄, filtered and concentrated. Crystallization of the crude material from MeOH provided **518** (0.348 g, 28%): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.39 (s, 1 H), 7.72 (d, 1 H), 7.58-7.52 (m, 3 H), 2.59 (t, 2 H), 2.25 (s, 3 H), 2.07 (s, 3 H), 0.80-0.72 (m, 1 H), 0.34-0.29 (m, 2 H), 0.06-0.03 (m, 2 H).

Step B:



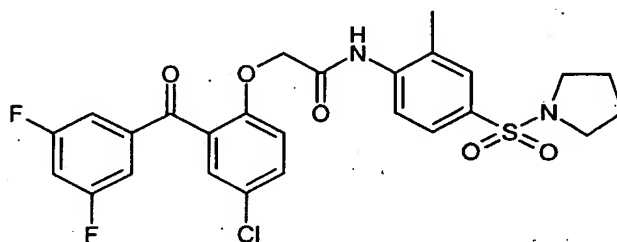
519

A mixture of **518** (0.310 g, 1.1 mmol) and 1.5 M HCl (2.5 mL) in 12 mL of ethanol was heated to 80 °C for 18 h. The reaction mixture was then poured into 50 mL of saturated NaHCO₃ (aq) and extracted with two 30-mL portions of CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo* to afford **519**, which was used without further purification (0.284 g): MS (ES+) *m/z* 241 (M+H); ¹H NMR (CDCl₃, 400 MHz) δ 7.54-7.51 (m, 2 H), 6.68 (d, 1 H), 4.41 (t, 1 H), 4.06 (br s, 2 H), 2.78 (t, 2 H), 2.18 (s, 3 H), 0.92-0.83 (m, 1 H), 0.48-0.43 (m, 2 H), 0.11-0.07 (m, 2 H).

Step C:

Acid 49 was converted to the acid chloride using the general procedure V. Aniline 519 (0.07 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to afford 517 as an off-white solid (0.129 g, 81%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.1 (m, 2H), 0.36 (m, 2H), 0.82 (m, 1H), 2.2 (s, 3H), 2.64 (t, 2H), 4.86 (s, 2H), 7.25 (d, 1H), 7.46-7.74 (m, 9H), 9.44 (s, 1H); MS (ES⁺) *m/z* 549 (M+H)⁺, MS (ES⁻) *m/z* 547 (M-H)⁻.

Example 212:

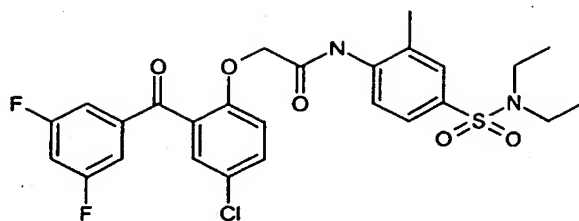


520

Acid 49 was converted to the acid chloride using the general procedure V. Aniline 318 (0.07 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to afford 520 as an off-white solid (0.126 g, 79%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.66 (m, 4H), 2.26 (s, 3H), 3.35 (m, 4H), 4.87 (s, 2H), 7.25 (d, 1H), 7.47-7.7 (m, 7H), 7.82 (d, 1H), 9.43 (s, 1H); MS (ES⁺) *m/z* 549 (M+H)⁺, MS (ES⁻) *m/z* 547 (M-H)⁻.

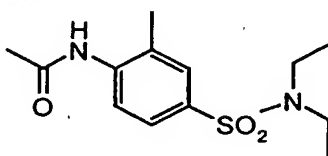
Example 213:

314



521

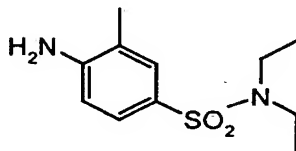
Step A:



522

A mixture of **464** (1.10 g, 4.4 mmol), diethylamine (0.68 mL, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in 50 mL of methylene chloride was stirred at rt for 5 d. The reaction mixture was then diluted with 100 mL of CH_2Cl_2 and washed with two 50-mL portions of water. The organic layer was washed with brine, dried over MgSO_4 , and filtered to give 1.2 g of an orange oil. Crystallization from EtOAc /hexane gave **522** as orange crystals (0.446 g, 36%): MS (ES+) m/z 285 (M+H); ^1H NMR (CDCl_3 , 400 MHz) δ 8.08 (d, 1 H), 7.61-7.58 (m, 2 H), 3.21 (q, 4 H), 2.29 (s, 3 H), 2.24 (s, 3 H), 1.13 (t, 6 H).

Step B:



523

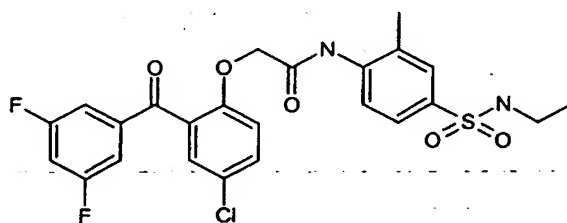
A mixture of **522** (0.341 g, 1.2 mmol) and 1.5 M HCl (2.5 mL) in 12 mL of ethanol was heated to 80 °C for 18 h. The reaction mixture was then poured into 50 mL of saturated NaHCO_3 (aq) and extracted with two 30-mL portions of CH_2Cl_2 . The combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo* to give **523** as a yellow

solid (0.285 g, 98%): MS (ES⁺) m/z 243 (M+H); ¹H NMR (CDCl₃, 400 MHz) δ 7.48-7.45 (m, 2 H), 6.66 (d, 1 H), 4.02 (br s, 2 H), 3.19 (q, 4 H), 2.18 (s, 3 H), 1.12 (t, 6 H).

Step C:

- 5 Acid 49 was converted to the acid chloride using the general procedure V. Aniline 523 (0.07 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to afford 521 as an off-white solid (0.117 g, 73%). ¹H NMR (DMSO-
10 d_6 , 300 MHz) δ 1.06 (t, 6H), 2.24 (s, 3H), 3.16 (m, 4H), 4.86 (s, 2H), 7.25 (d, 1H), 7.47-7.70 (m, 7H), 7.77 (d, 1H), 9.43 (s, 1H); MS (ES⁺) m/z 551 (M+H)⁺, MS (ES⁻) m/z 549 (M-H)⁻.

Example 214:



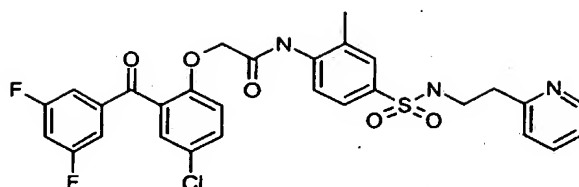
15

524

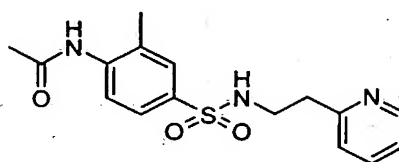
- Acid 49 was converted to the acid chloride using the general procedure V. Aniline 312 (0.062 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL)
20 was added to the reaction mixture and the resulting suspension was filtered. The solid was washed with ether to afford 524 as an off-white solid (0.109 g, 70%). ¹H NMR (DMSO- d_6 , 400 MHz) δ 0.99 (t, 3H), 2.23 (s, 3H), 2.77 (m, 2H), 4.86 (s, 2H), 7.25 (d, 1H), 7.46-7.75 (m, 9H), 9.45 (s, 1H); MS (ES⁺) m/z 523 (M+H)⁺, MS (ES⁻) m/z 521 (M-H)⁻.

Example 215:

316



525

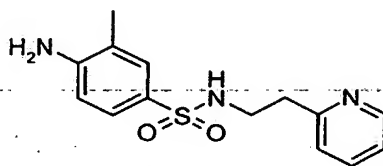


526

5 **Step A:**

Sulfonyl chloride **464** (0.27 g, 1.09 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and 2-(2-aminoethyl)pyridine (Aldrich, 0.28 g, 2.3 mmol). The mixture was allowed to stir for 2 d. Water was added and the mixture was extracted with dichloromethane, concentrated, and purified by flash chromatography using 95:5

10 $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$ as eluant to afford **526** (0.70 g, 51%). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 2.05 (s, 3H), 2.22 (s, 3H), 2.77 (t, 2H), 3.03 (t, 2H), 7.13 (dd, 2H), 7.48-7.71 (m, 5H), 8.38 (dd, 1H), 9.37 (s, 1H).



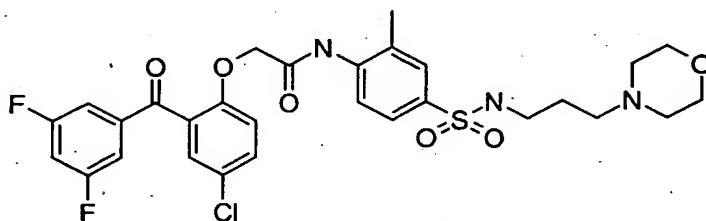
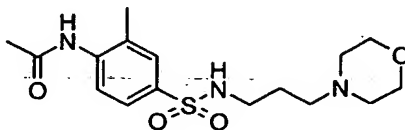
527

15 **Step B:**

Sulfonamide **526** (0.7 g, 2.09 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford **527** (0.11 g, 18%). The crude product was used without further purification.

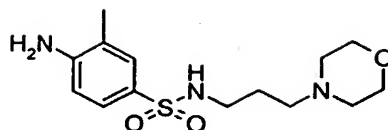
Step C:

Acid **49** was converted to the acid chloride using the general procedure V. Aniline **527** (0.05 g, 0.17 mmol), the acid chloride (0.19 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) were used as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **525** (0.03 g, 33%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.18 (s, 3H), 2.81 (t, 2H), 3.08 (m, 2H), 4.83 (s, 2H), 7.16-7.23 (m, 3H), 7.43-7.7 (m, 10H), 8.42 (m, 1H), 9.41 (s, 1H); MS (ES⁺) *m/z* 600 (M+H)⁺, MS (ES⁻) *m/z* 598 (M-H)⁻.

Example 216:**528****Step A:****529**

Sulfonyl chloride **464** (0.27 g, 1.09 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and aminopropylmorpholine (Aldrich, 0.33 g, 2.3 mmol). The mixture was allowed to stir for 2 d, followed by the addition of water and extraction with dichloromethane. The organic layer was concentrated, and the product purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **529** (0.7 g, 49%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 1.44 (m, 2H), 2.05 (s, 3H), 2.12 (m, 4H), 2.23 (s, 2H), 2.7 (m, 2H), 3.45 (m, 4H), 7.41 (t, 1H), 7.5 (dd, 1H), 7.55 (d, 1H), 7.71 (d, 1H), 9.38 (s, 1H).

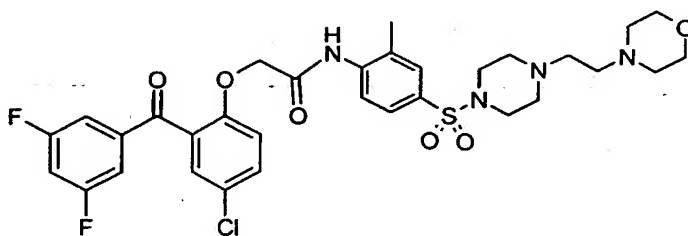
318

Step B:**530**

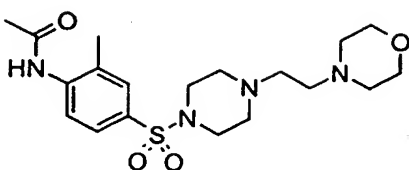
- 5 Sulfonamide **529** (0.7 g, 1.96 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford **530** (0.15 g, 24%). The crude product was used without further purification.

Step C:

- 10 Acid **49** was converted to the acid chloride using the general procedure V. Aniline **530** (0.05 g, 0.16 mmol), the acid chloride (0.19 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) were used as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The product was purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **528**
- 15 (0.01 g, 6%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 0.8 (m, 1H), 1.18 (s, 1H), 1.43 (m, 2H), 2.15 (m, 7H), 2.7 (m, 2H), 3.44 (m, 4H), 4.78 (s, 2H), 7.18 (d, 1H), 7.39-7.67 (m, 9H), 9.38 (s, 1H); LC-MS (ES⁺) *m/z* 623 (M+H)⁺, MS (ES⁻) *m/z* 621 (M-H)⁻.

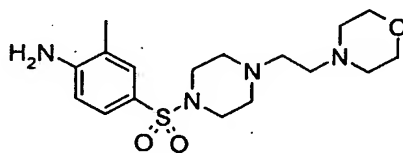
Example 217:**531****Step A:**

319



532

Sulfonyl chloride **464** (0.27 g, 1.09 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and 1-(2-morpholinoethyl)piperazine (EMKA, 0.46 g, 2.3 mmol). The mixture was allowed to stir for 2 , followed by the addition of and extraction with dichloromethane. The organic layer was concentrated, and the product was purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **532** (0.3 g, 19%).
¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.07 (s, 3H), 2.27 (m, 9H), 2.38 (m, 2H), 2.45 (m, 4H), 2.85 (m, 2H), 3.3 (m, 2H), 3.5 (m, 4H), 7.46 (m, 2H), 7.82 (d, 1H), 9.4 (s, 1H).

Step B:

533

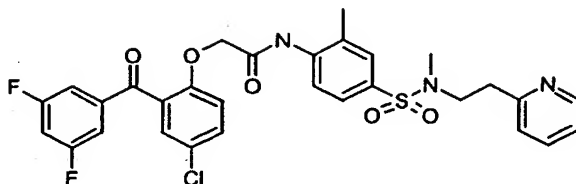
Sulfonamide **532** (0.3 g, 0.73 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford **533** (0.08 g, 30%). The crude product was used without further purification.

Step C:

Acid **49** was converted to the acid chloride using the general procedure V. Aniline **533** (0.05 g, 0.14 mmol), the acid chloride (0.19 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) were used as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The product was purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **531** (0.01 g, 7%).
¹H NMR (CDCl₃, 400 MHz) δ 2.29 (s, 3H), 2.38-2.54 (m, 12H), 2.97 (bs,

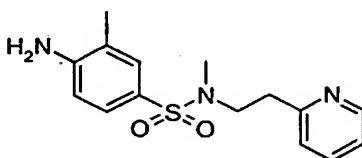
4H), 3.63 (m, 4H), 4.69 (s, 2H), 7-7.1 (m, 2H), 7.29-7.35 (m, 3H), 7.51-7.57 (m, 3H), 8.1 (d, 1H), 8.66 (s, 1H).

Example 218:



534

Step A:



535

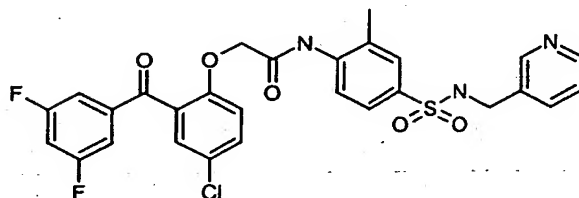
- 10 Sulfonyl chloride 464 (3 mmol), pyridine (5 mL), and 2-(2-methylaminoethyl)pyridine (Aldrich, 0.41 g, 3.01 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 d. Water was added and the mixture was extracted with dichloromethane, and the organic layer was concentrated in vacuo. The resulting products were then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C
- 15 overnight. The resulting solution was concentrated in vacuo and the product was purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford 535 (0.28 g, 30%).

Step B:

- Acid 49 was converted to the acid chloride using the general procedure V. Aniline 535 (0.05 g, 0.16 mmol), the acid chloride (0.15 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) were used as in general procedure VI. Ice (5 mL)
- 20 was added to the reaction mixture and the resulting suspension was filtered. The solid was then purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford 534 (0.04 g, 40%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.21 (s, 3H), 2.67 (s, 3H), 2.93 (m, 2H),

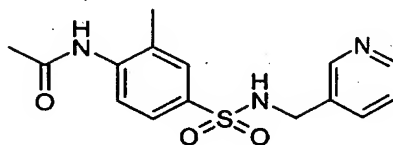
4.08 (m, 2H), 4.83 (s, 2H), 7.18-7.27 (m, 3H), 7.43-7.77 (m, 9H), 8.46 (m, 1H), 9.41 (s, 1H); LC-MS (ES^+) m/z 614 ($\text{M}+\text{H}^+$), LC-MS (ES^-) m/z 612 ($\text{M}-\text{H}^-$).

Example 219:



536

Step A:

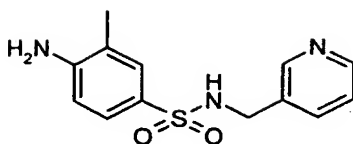


537

Sulfonyl chloride 464 (3 mmol), pyridine (5 mL), and 3-picolylamine (Aldrich, 0.25 g, 2.3 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 d followed by the addition of water. The reaction mixture was extracted with dichloromethane, and the organic layer was separated and concentrated in vacuo. The product was purified by flash chromatography using 95:5 CH_2Cl_2 : CH_3OH as eluant to afford **537** (0.9 g, 67%). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 2.06 (s, 3H), 2.22 (s, 3H), 3.96 (d, 2H), 7.24 (dd, 1H), 7.54 (m, 3H), 7.71 (d, 1H), 8.06 (t, 1H), 8.36 (d, 2H), 9.37 (s, 1H).

Step B:

322

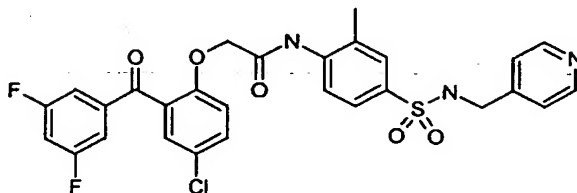


538

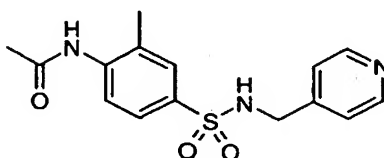
Sulfonamide 537 (0.9 g, 2.81 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford 538 (0.25 g, 32%). The crude product was used without further purification.

Step C:

Acid 49 was converted to the acid chloride using the general procedure V. Aniline 538 (0.05 g, 0.18 mmol), the acid chloride (0.15 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The product was purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford 536 (0.03 g, 27%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.18 (s, 3H), 4 (d, 2H), 4.83 (s, 2H), 7.22 (d, 1H), 7.28 (dd, 1H), 7.45 (m, 2H), 7.51 (d, 1H), 7.57-7.72 (m, 6H), 8.13 (t, 1H), 8.41 (m, 2H), 9.42 (s, 1H); LC-MS (ES⁺) *m/z* 586 (M+H)⁺, LC-MS (ES⁻) *m/z* 584 (M-H)⁻.

Example 220:

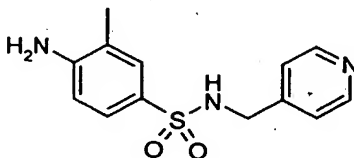
539

Step A:

323

540

Sulfonyl chloride **464** (1.1 mmol), pyridine (5 mL), and 4-picolylamine (Aldrich, 0.25 g, 2.3 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 d followed by the addition of water. The mixture was extracted with dichloromethane, the organic layer was separated and concentrated in vacuo. The product was purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **540** (0.5 g, 37%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.06 (s, 3H), 2.21 (s, 3H), 3.95 (d, 2H), 7.21 (d, 2H), 7.52 (m, 2H), 7.71 (m, 1H), 8.14 (t, 1H), 8.41 (dd, 2H), 9.38 (s, 1H).

Step B:

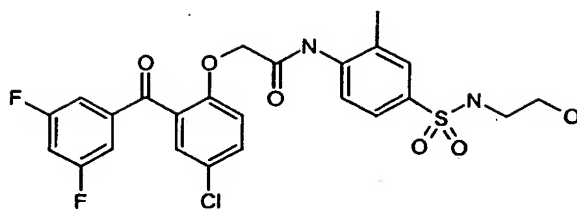
Sulfonamide **540** (0.5 g, 1.56 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford **541** (0.12 g, 28%). The crude product was used without further purification.

Step C:

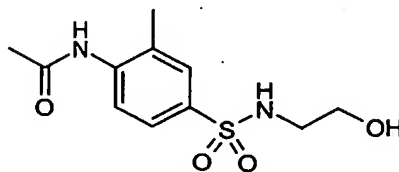
Acid **49** was converted to the acid chloride using the general procedure V. Aniline **541** (0.05 g, 0.18 mmol), the acid chloride (0.15 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The product was purified by flash chromatography and TLC prep plate using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **539** (0.02 g, 19%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.18 (s, 3H), 4.01 (m, 2H), 4.83 (s, 2H), 7.21-7.26 (m, 3H), 7.43-7.72 (m, 8H), 8.2 (t, 1H), 8.45 (m, 2H), 9.42 (s, 1H); LC-MS (ES⁺) *m/z* 586 (M+H)⁺, LC-MS (ES⁻) *m/z* 584 (M-H)⁻.

Example 221:

324

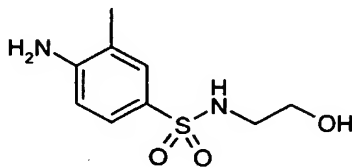


542

Step A:

543

Sulfonyl chloride **464** (1.1 mmol), pyridine (5 mL), and ethanolamine (Aldrich, 0.14 g, 2.3 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 d followed by the addition of water. The mixture was extracted with dichloromethane, the organic layer was separated and concentrated in vacuo. The product was purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **543** (0.46 g, 37%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.05 (s, 3H), 2.23 (s, 3H), 2.7 (m, 2H), 3.29 (m, 2H), 4.62 (t, 1H), 7.41 (t, 1H), 7.51 (dd, 1H), 7.56 (d, 1H), 7.7 (d, 1H), 9.38 (s, 1H).

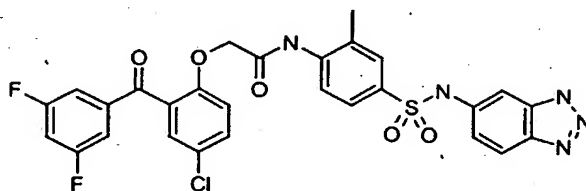
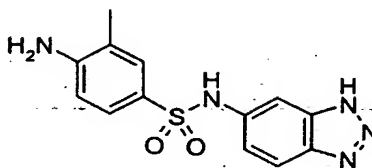
Step B;

544

Sulfonamide **549** (0.46 g, 1.68 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford **544** (0.12 g, 31%). The crude product was used without further purification.

Step C:

Acid **49** was converted to the acid chloride using the general procedure V. Aniline **544** (0.05 g, 0.22 mmol), the acid chloride (0.15 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The product was purified by flash chromatography and TLC prep plate using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **542** (0.02 g, 17%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.2 (s, 3H), 2.75 (q, 2H), 3.34 (m, 2H), 4.66 (t, 1H), 4.83 (s, 2H), 7.22 (d, 1H), 7.42-7.72 (m, 9H), 9.42 (s, 1H); LC-MS (ES⁺) *m/z* 539 (M+H)⁺, LC-MS (ES⁻) *m/z* 537 (M-H)⁻.

Example 222:**545****Step A:****546**

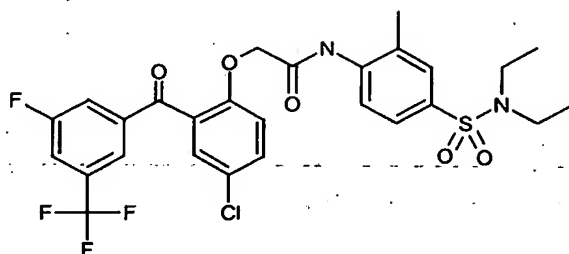
Sulfonyl chloride **464** (3 mmol), pyridine (5 mL), and 5-aminobenzotriazole (Lancaster, 0.41 g, 3.06 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 days. Water was added and the mixture was extracted with dichloromethane, the organics were separated, concentrated in vacuo. The resulting products were then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated, with stirring, to 60 °C overnight. The resulting solution was concentrated in vacuo and purified by flash

chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **546** (0.45 g, 48%). The crude product was used without further purification.

Step B:

- 5 Acid **49** was converted to the acid chloride using the general procedure V. Aniline **546** (0.05 g, 0.16 mmol), the acid chloride (0.15 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were then purified by flash chromatography and TLC prep plate using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **545** (0.01 g, 10%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.13 (s, 3H), 4.78 (s, 2H), 7.16 (m, 2H), 7.39-7.85 (m, 11H), 9.34 (s, 1H) 10.5 (bs, 1H); LC-MS (ES⁺) *m/z* 586 (M+H)⁺, LC-MS (ES⁻) *m/z* 584 (M-H)⁻.
- 10

Example 223:



15

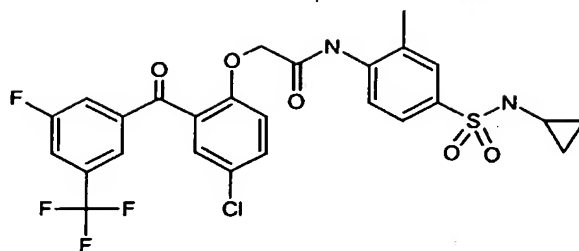
547

- Acid **71** was converted to the acid chloride using the general procedure V. Aniline **523** (0.1 g, 0.41 mmol), the acid chloride (0.16 g, 0.4 mmol), acetone (4 mL), and sodium bicarbonate (0.22 g, 2.6 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford **547** (0.085 g, 34%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.02 (t, 6H), 2.18 (s, 3H), 3.12 (m, 4H), 4.81 (s, 2H), 7.22 (d, 1H), 7.54-7.71 (m, 5H), 7.87 (d, 2H), 7.98 (d, 1H), 9.38 (s, 1H); LC-MS (ES⁺) *m/z* 601 (M+H)⁺, LC-MS (ES⁻) *m/z* 599 (M-H)⁻.
- 20

Example 224:

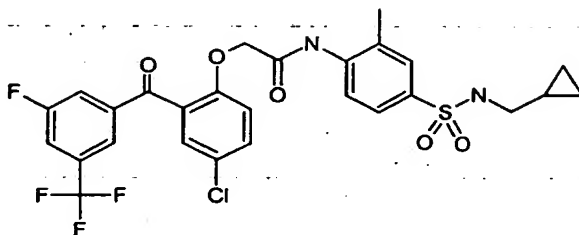
25

327



548

Acid 71 was converted to the acid chloride using the general procedure V. Aniline 315 (0.1 g, 0.44 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.4 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography and TLC prep plate using 98:2 CH₂Cl₂:CH₃OH as eluant to afford 548 (0.074 g, 29%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.3-0.5 (m, 4H), 2.04 (m, 1H), 2.18 (s, 3H), 4.81 (s, 2H), 7.24 (d, 1H), 7.54-7.88 (m, 8H), 8 (d, 1H), 9.41 (s, 1H); LC-MS (ES⁺) *m/z* 585 (M+H)⁺, LC-MS (ES⁻) *m/z* 583 (M-H)⁻.

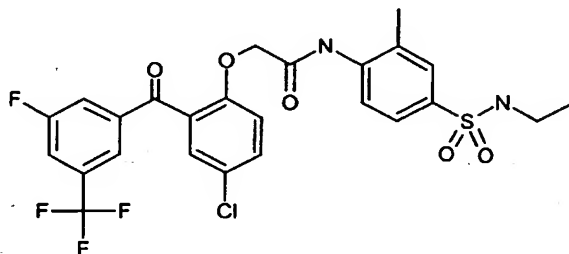
Example 225:

549

Acid 71 was converted to the acid chloride using the general procedure V. Aniline 518 (0.1 g, 0.42 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.4 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford 549 (0.095 g, 38%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.05 (m, 2H), 0.33 (m, 2H), 0.77 (m, 1H), 2.16 (s, 3H), 2.6

(d, 2H), 4.8 (s, 2H), 7.22 (d, 1H), 7.54-7.67 (m, 6H), 7.86 (d, 2H), 8 (d, 1H), 9.4 (s, 1H); LC-MS (ES⁺) *m/z* 599 (M+H)⁺, LC-MS (ES⁻) *m/z* 597 (M-H)⁻.

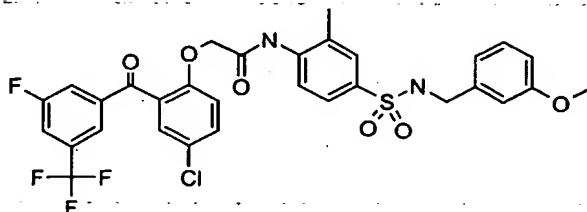
Example 225:



550

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **312** (0.1 g, 0.42 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.4 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford **550** (0.125 g, 47%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.94 (t, 3H), 2.17 (s, 3H), 2.72 (m, 2H), 4.81 (s, 2H), 7.22 (d, 1H), 7.43 (t, 1H), 7.53-7.68 (m, 5H), 7.87 (d, 2H), 8 (d, 1H), 9.4 (s, 1H); LC-MS (ES⁺) *m/z* 573 (M+H)⁺, LC-MS (ES⁻) *m/z* 571 (M-H)⁻.

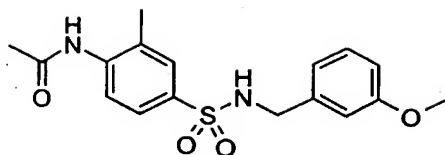
Example 226:



551

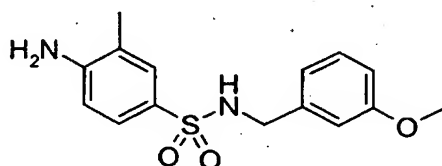
Step A:

329



552

Sulfonyl chloride 464 (3 mmol), pyridine (5 mL), and 3-methoxybenzylamine (Aldrich, 0.41 g, 3.01 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 d. The resulting mixture was concentrated in vacuo. Water was added and the mixture was filtered to afford 552 (0.24 g, 69%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.06 (s, 3H), 2.21 (s, 3H), 3.63 (s, 3H), 3.89 (d, 2H), 6.73 (m, 3H), 7.13 (t, 1H), 7.53 (m, 2H), 7.7 (d, 1H), 7.96 (t, 1H), 9.36 (s, 1H); LC-MS (ES⁺) *m/z* 349 (M+H)⁺, LC-MS (ES⁻) *m/z* 347 (M-H)⁻.

Step B:

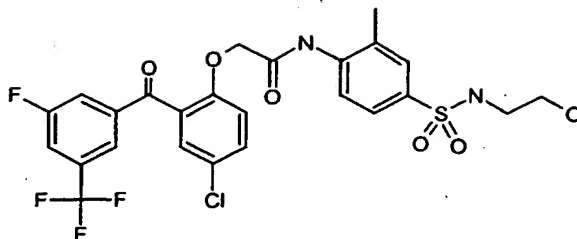
553

The sulfonamide 552 was dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL). The resulting mixture was heated to 60 °C overnight. The resulting solution was concentrated in vacuo to afford 553. The product was used without further purification.

Step C:

Acid 71 was converted to the acid chloride using the general procedure V. Aniline 553 (0.1 g, 0.33 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford 551 (0.212 g, 98%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.14 (s, 3H), 3.66 (s, 3H), 3.92 (d, 2H), 4.81 (s, 2H), 6.77 (t, 3H), 7.13-7.24 (m, 2H), 7.55 (m, 3H), 7.66 (dd, 2H), 7.87 (m, 2H), 8.02 (t, 2H), 9.4 (s, 1H); LC-MS (ES⁺) *m/z* 665 (M+H)⁺, LC-MS (ES⁻) *m/z* 663 (M-H)⁻.

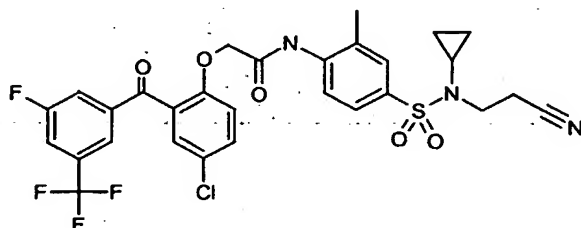
330

Example 227:

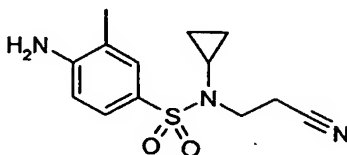
554

Acid 71 was converted to the acid chloride using the general procedure V. Aniline 544
 5 (0.1 g, 0.43 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid
 chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the
 resulting solutions were concentrated, re-dissolved in dichloromethane and purified by
 flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford 554 (0.073 g, 29%).

¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.17 (s, 3H), 2.74 (m, 2H), 3.35 (m, 2H), 4.65 (t, 1H),
 10 4.81 (s, 2H), 7.22 (d, 1H), 7.45-7.68 (m, 6H), 7.87 (d, 2H), 8 (d, 1H), 9.41 (s, 1H); LC-MS
 (ES⁺) *m/z* 589 (M+H)⁺, LC-MS (ES⁻) *m/z* 587 (M-H)⁻.

Example 228:

555

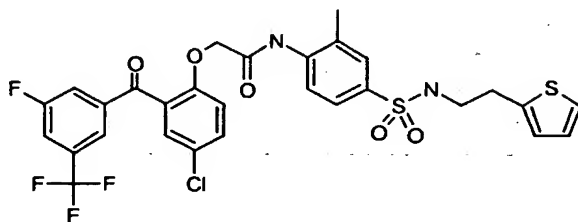
Step A:

556

Sulfonyl chloride **464** (3 mmol), pyridine (5 mL), and 3-(cyclopropylamino)propionitrile (Trans World Chemical, 0.33 g, 3 mmol) were used as in general procedure XXVI. The mixture was allowed to stir for 2 d, followed by the addition of water and extraction with dichloromethane. The organic layer was separated and concentrated in vacuo. The resulting products were then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solution was concentrated in vacuo and the product purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **556** (0.22 g, 26%).

Step B:

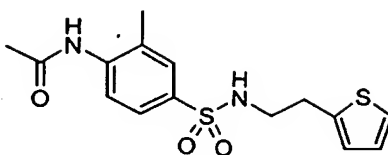
Acid **71** was converted to the acid chloride using the general procedure V. Aniline **556** (0.1 g, 0.36 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solution was concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford **556** (0.113 g, 49%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.63-0.82 (m, 4H), 2 (m, 1H), 2.21 (s, 3H), 2.78 (t, 2H), 3.36 (m, 2H), 4.82 (s, 2H), 7.22 (d, 1H), 7.54 (d, 1H), 7.63 (m, 3H), 7.79 (d, 1H), 7.87 (d, 2H), 8 (d, 1H), 9.42 (s, 1H); LC-MS (ES⁺) *m/z* 638 (M+H)⁺, LC-MS (ES⁻) *m/z* 638 (M-H)⁻

Example 229:

557

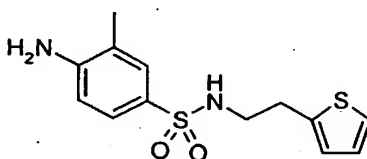
Step A:

332



558

Sulfonyl chloride 464 (3 mmol), pyridine (5 mL), and thiophene-2-ethylamine (Aldrich, 0.41 g, 3.01 mmol) were used as in general procedure XVI. The mixture was allowed to stir at rt for 2 d, followed by concentration in vacuo. Water was added to the resulting residue and the mixture was filtered to afford the protected sulfonamide 558 (0.12 g, 35%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.05 (s, 3H), 2.23 (s, 3H), 2.81-2.93 (m, 4H), 6.79 (d, 1H), 6.87 (dd, 1H), 7.26 (dd, 1H), 7.51 (dd, 1H), 7.55 (s, 1H), 7.61 (t, 1H), 7.71 (d, 1H), 9.37 (s, 1H); LC-MS (ES⁺) *m/z* 339 (M+H)⁺, LC-MS (ES⁻) *m/z* 337 (M-H)⁻.

Step B:

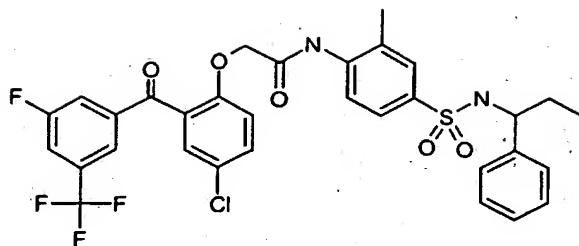
559

Sulfonamide 558 was dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solutions were concentrated in vacuo to afford 559. The resulting product was used without further purification.

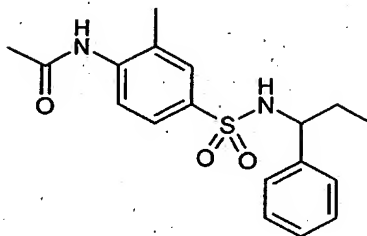
Step C:

Acid 71 was converted to the acid chloride using the general procedure V. Aniline 559 (0.1 g, 0.34 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford 557 (0.206 g, 93%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.16 (s, 3H), 2.87-2.95 (m, 4H), 4.8 (s, 2H), 6.83 (d, 1H), 6.91 (t, 1H), 7.22 (d, 1H), 7.3 (d, 1H), 7.54-7.68 (m, 6H), 7.87 (d, 2H), 8 (d, 1H), 9.4 (s, 1H); LC-MS (ES⁺) *m/z* 654 (M+H)⁺, LC-MS (ES⁻) *m/z* 653 (M-H)⁻.

333

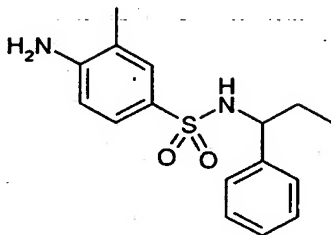
Example 230:

560

Step A:

561

Sulfonyl chloride **464** (3 mmol), pyridine (5 mL), and DL-1-phenylpropylamine (Norse, 0.41 g, 3.01 mmol) were used as in general procedure XXVI. The mixture was allowed to stir at rt for 2 d, followed by concentration in vacuo. Water was added to the resulting residue and the mixture was filtered to afford the protected sulfonamide **561** (0.19 g, 55%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 0.61 (t, 3H), 1.5 (m, 2H), 2.03 (s, 3H), 2.08 (s, 3H), 4.03 (m, 1H), 7.03-7.12 (m, 5H), 7.26 (d, 1H), 7.35 (dd, 1H), 7.56 (d, 1H), 8 (d, 1H), 9.24 (s, 1H); LC-MS (ES⁺) *m/z* 347 (M+H)⁺, LC-MS (ES⁻) *m/z* 345 (M-H)⁻.

Step B:

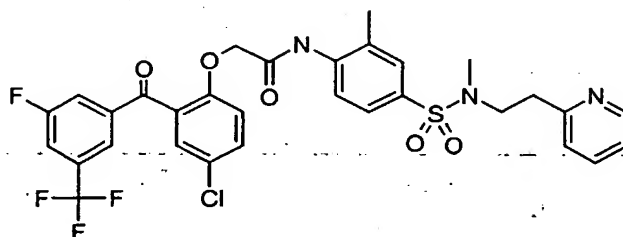
562

Sulfonamide 561 was dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solution was concentrated in vacuo to afford 562. The resulting product was used without further purification.

5 **Step C:**

Acid 71 was converted to the acid chloride using the general procedure V. Aniline 562 (0.1 g, 0.33 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solution was concentrated, re-dissolved in dichloromethane and purified by flash
10 chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford 560 (0.185 g, 85%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.63 (t, 3H), 1.55 (m, 2H), 2 (s, 3H), 4.06 (m, 1H), 4.85 (s, 2H), 7.04-7.15 (m, 5H), 7.22 (d, 1H), 7.3 (s, 1H), 7.39 (dd, 1H), 7.53 (m, 2H), 7.66 (dd, 1H), 7.87 (d, 2H), 7.99-8.07 (m, 2H), 9.29 (s, 1H); LC-MS (ES⁺) *m/z* 663 (M+H)⁺, LC-MS (ES⁻) *m/z* 661 (M-H)⁻.

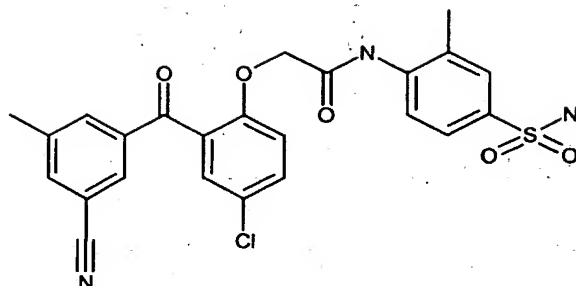
15 **Example 231:**



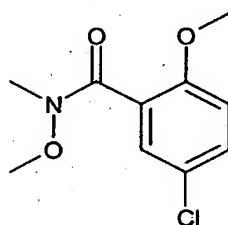
563

Acid 71 was converted to the acid chloride using the general procedure V. Aniline 535 (0.1 g, 0.33 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solution was concentrated, re-dissolved in dichloromethane and purified by flash
20 chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford 563 (0.193 g, 89%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.21 (s, 3H), 2.67 (s, 3H), 2.92 (t, 2H), 4.09 (m, 2H), 4.83 (s, 2H), 7.18-7.27 (m, 3H), 7.42-7.78 (m, 9H), 8.46 (m, 1H), 9.41 (s, 1H); LC-MS (ES⁺)
25 *m/z* 664 (M+H)⁺, LC-MS (ES⁻) *m/z* 662 (M-H)⁻.

335

Example 232:

564

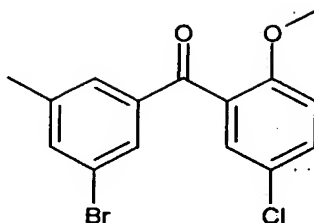
Step A:

565

5-Chloro-2-methoxybenzoic acid (Aldrich, 17.1 g, 91 mmol), oxalyl chloride (50 mL of 2.0 M solution in dichloromethane, 100 mmol), DMF (1.2 mL), and dichloromethane (100 mL), were used to prepare the acid chloride according to general procedure V. The mixture was concentrated after 2 h, dissolved in chloroform (50 mL), and added dropwise to a solution of N,O-dimethylhydroxylamine (Aldrich, 13.34 g, 140 mmol), chloroform (200 mL), and triethylamine (19.06 mL, 140 mmol) at 0 °C as in general procedure VII. After 1 h, water was added to the reaction mixture and the organic layer was separated. The aqueous was further extracted with ethyl acetate. The organic layers were combined, dried over MgSO₄, filtered and the solvents were removed under reduced pressure to afford **565** (18.69 g, 96%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.2 (bs, 3H), 3.45 (bs, 3H), 3.77 (s, 3H), 7.1 (d, 1H), 7.3 (d, 1H), 7.42 (m, 1H).

Step B:

336

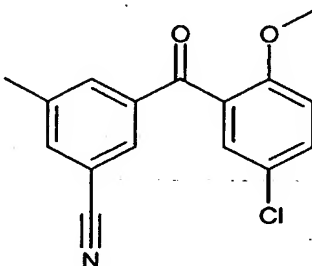


566

Into a oven dried round-bottom flask equipped with a stir bar, nitrogen on demand, and an addition funnel, were added 3,5-dibromotoluene (Avocado, 20.85 g, 83.4 mmol), and methyl t-butyl ether (500 mL) and the mixture was cooled to -50°C by means of an acetonitrile dry ice bath. *n*-Butyllithium (57.4 mL of a 1.6 M solution in hexanes, 91.8 mmol) was added dropwise to the reaction and the mixture was allowed to stir for 30 min at -50°C . Weinreb amide 565 (19.16 g, 83.4 mmol) was added portionwise via a powder addition funnel. The mixture was allowed to stir at -50°C , then warm to rt overnight.

When judged to be complete, the reaction was poured into saturated ammonium chloride (500 mL) and stirred vigorously for 30 min. The mixture was then added to a separatory funnel. The organics were collected, washed with water, brine, dried over MgSO_4 , filtered, and concentrated in vacuo to give a yellow solid (28.64 g) that was pulverized, then triturated with methanol and filtered to give 566 as a pale yellow solid (19.2 g, 68%).

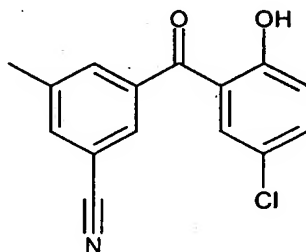
$^1\text{H NMR}$ ($\text{DMSO}-d_6$, 400 MHz) δ 2.29 (s, 3H), 3.63 (s, 3H), 7.18 (d, 1H), 7.36 (d, 1H), 7.42 (s, 1H), 7.55 (m, 2H), 7.66 (s, 1H).

Step C:

567

Into a oven dried round-bottom flask equipped with a stir bar, nitrogen on demand, and a reflux condenser, were added 566 (4.02 g, 12 mmol), sodium cyanide (1.16 g, 24 mmol),

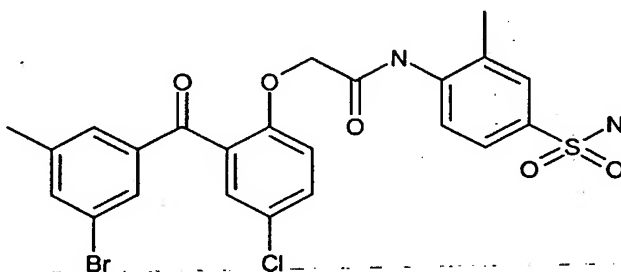
copper iodide (0.26 g, 1.4 mmol), and propionitrile (50 mL degassed with nitrogen for 30 min). To this mixture was added $\text{Pd}(\text{PPh}_3)_4$ (Strem, 1.37 g, 1.2 mmol) that had been triturated with methanol and filtered prior to addition. The mixture was heated to reflux and allowed to stir for 30 min. The mixture was cooled to rt and ethyl acetate (100 mL) was added. The resulting suspension was filtered through celite and the solids washed with ethyl acetate. The filtrate was washed with water, brine, dried over MgSO_4 , filtered, and concentrated in vacuo. The resulting product was further purified by flash chromatography using 4:1 hexanes: ethyl acetate to afford **567** as an off-white solid (3.33 g, 99%). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 2.44 (s, 3H), 3.69 (s, 3H), 7.26 (d, 1H), 7.46 (d, 1H), 7.66 (dd, 1H), 7.86 (d, 2H), 7.99 (s, 1H).

Step D:**568**

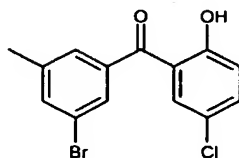
Anisole derivative **567** (3.27 g, 14.2 mmol), dichloromethane (45 mL), and boron tribromide (1.41 mL in 15 mL of dichloromethane) were combined as described in general procedure IX. The reaction was stirred at -78°C for 1 h then allowed to warm to rt and stir for an additional 4 h. The reaction was then poured into ice water (500 mL) and stirred for additional 45 min, and poured into a separatory funnel. The organic layers were collected and washed with water, brine, and dried over MgSO_4 , filtered, and concentrated in vacuo to give a yellow solid (5.62 g). The resulting solid that was recrystallized from methanol and filtered to give **568** as pale yellow crystals (2.65 g, 85%). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 2.4 (s, 3H), 6.98 (d, 1H), 7.37 (d, 1H), 7.47 (dd, 1H), 7.82 (d, 1H), 7.87 (s, 1H), 7.93 (d, 1H), 10.43 (s, 1H).

Step E:

Compound **568** (2.65 g, 9.8 mmol), potassium carbonate (6.74 g, 49 mmol), compound **470** (3.14 g, 10 mmol), and acetone (50 mL) were combined in a round-bottom flask, and heated to reflux for 4 h. The reaction was concentrated in vacuo, then water (200 mL) and dichloromethane were added and the suspension was filtered. The filtrate was poured in a separatory funnel and separated. The organic layer was collected, washed with saturated sodium bicarbonate solution, water, brine, dried over MgSO_4 , filtered and concentrated in vacuo. The resulting solid was further purified by flash chromatography using 1:1 hexanes:ethyl acetate as eluant to afford an off-white solid. The solid was recrystallized from acetonitrile and water to afford **564** (1.61 g, 66%). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 2.17 (s, 3H), 2.37 (s, 3H), 4.81 (s, 2H), 7.24 (m, 3H), 7.5 (d, 1H), 7.58-7.66 (m, 4H), 7.92 (d, 2H), 7.98 (s, 1H), 9.39 (s, 1H).

Example 233:

15

569**Step A:****570**

Anisole derivative **566** (1.02 g, 3 mmol), dichloromethane (10 mL), and boron tribromide (3 mL of a 1 M solution in dichloromethane) were combined as described in general procedure IX. The reaction was stirred at -78°C for 90 min, and was then allowed to warm to rt and stir for an additional 1 h. Water (100 mL) was added to the reaction and

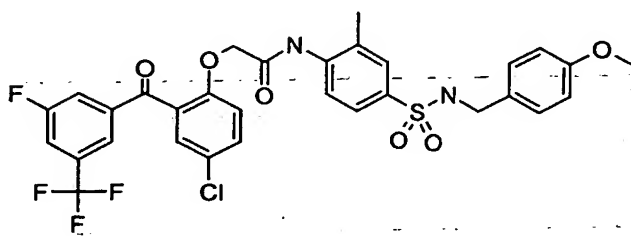
20

the resulting mixture was stirred for 30 min. The mixture was then added to a separatory funnel, the organic layer was collected, dried over MgSO_4 , filtered, and concentrated in vacuo to afford **570** as a pale yellow solid (0.965 g, 99%). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 2.34 (s, 3H), 6.96 (d, 1H), 7.33 (d, 1H), 7.45 (m, 2H), 7.58 (s, 1H), 7.69 (s, 1H), 10.37 (s, 1H).

Step B:

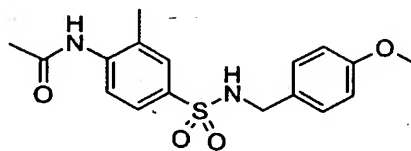
Compound **570** (0.16 g, 0.5 mmol), potassium carbonate (0.34 g, 2.5 mmol), compound **470** (0.166 g, 0.54 mmol), and acetone (5 mL) were combined in a round-bottom flask, and heated to reflux overnight. Water was added, the resulting suspension was filtered and the solids purified by flash chromatography using 9:1 CH_2Cl_2 : CH_3OH as eluant to afford **569** as an off-white solid (0.035 g, 13%). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 2.16 (s, 3H), 2.3 (s, 3H), 4.8 (s, 2H), 7.24 (m, 3H), 7.46 (d, 1H), 7.58-7.68 (m, 6H), 9.29 (s, 1H).

Example 234:



571

Step A:

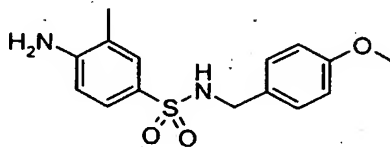


572

Sulfonyl chloride **464** (3 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and 4-methoxybenzylamine (Aldrich, 0.41 g, 3.01 mmol).

The mixture was allowed to stir for 2 d and was then concentrated in vacuo. Water was added to the remaining residue and the mixture was filtered. The filtrate was extracted with dichloromethane, the organic layer was collected, dried over MgSO_4 , filtered and concentrated in vacuo to afford the protected sulfonamide **572** (0.16 g, 46%). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 2.06 (s, 3H), 2.21 (s, 3H), 3.65 (s, 3H), 3.83 (d, 2H), 6.77 (dd, 2H), 7.08 (d, 2H), 7.52 (m, 2H), 7.7 (m, 1H), 7.87 (t, 1H), 9.36 (s, 1H); LC-MS (ES^+) m/z 349 ($\text{M}+\text{H}^+$), LC-MS (ES^-) m/z 347 ($\text{M}-\text{H}^-$).

Step B:



573

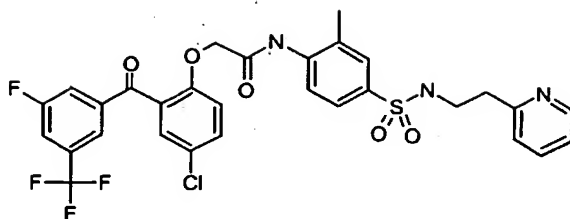
The sulfonamide was then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solution was concentrated in vacuo to afford **573**, which was used without further purification.

Step C:

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **573** (0.1 g, 0.33 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solution was concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2 : CH_3OH as eluant to afford **571** (0.070 g, 32%). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 2.15 (s, 3H), 3.69 (s, 3H), 3.87 (d, 2H), 4.82 (s, 2H), 6.8 (m, 2H), 7.1 (d, 2H), 7.23 (d, 1H), 7.56 (dd, 3H), 7.67 (m, 2H), 7.87-8.03 (m, 4H), 9.41 (s, 1H); LC-MS (ES^-) m/z 663 ($\text{M}-\text{H}^-$).

Example 235:

341



574

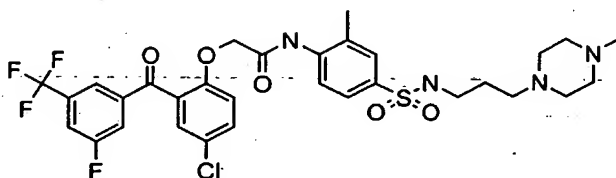
Acid **71** was converted to the acid chloride using the general procedure V. Aniline **527** (0.1 g, 0.34 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the

5 resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford **574** (0.040 g, 18%).

¹H NMR (DMSO-d₆, 300 MHz) δ 2.16 (s, 3H), 2.8 (dd, 2H), 3.08 (m, 2H), 4.81 (s, 2H), 7.16-7.25 (m, 3H), 7.53-7.69 (m, 7H), 7.88 (m, 2H), 8 (m, 1H), 8.42 (m, 1H), 9.4 (s, 1H);

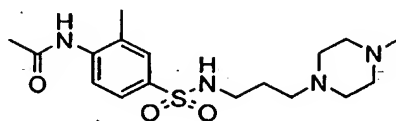
10 LC-MS (ES⁺) *m/z* 650 (M+H)⁺, LC-MS (ES⁻) *m/z* 648 (M-H)⁻.

Example 236:



575

Step A:



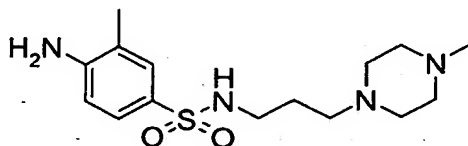
576

Sulfonyl chloride **464** (3 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and 1-(3-aminopropyl)-4-methylpiperazine (Aldrich, 0.48 g, 3.05 mmol).

20 The mixture was allowed to stir for 2 d, followed by concentration in vacuo. Water was

added to the remaining residue and the mixture was filtered. The filtrate was extracted with dichloromethane and the organic layer was collected, dried over MgSO_4 , filtered and concentrated in vacuo to afford the protected sulfonamide 576 (0.22 g, 20%), which was used without further purification.

5 **Step B:**



577

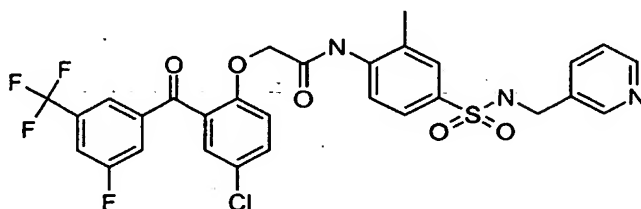
The sulfonamide 576 was then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solutions were concentrated in vacuo to afford 577. The resulting product was used without further purification.

Step C:

Acid 71 was converted to the acid chloride using the general procedure V. Aniline 577 (0.1 g, 0.31 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2 : CH_3OH as eluant to afford 575 (0.067 g, 32%).

^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 1.47 (m, 2H), 2.04-2.21 (m, 16H), 2.73 (m, 2H), 4.82 (s, 2H), 7.23 (d, 1H), 7.45-7.7 (m, 6H), 7.87 (m, 2H), 8.01 (m, 1H), 9.41 (s, 1H); LC-MS (ES^+) m/z 685 ($\text{M}+\text{H}^+$), LC-MS (ES^-) m/z 683 ($\text{M}-\text{H}^-$).

Example 237:



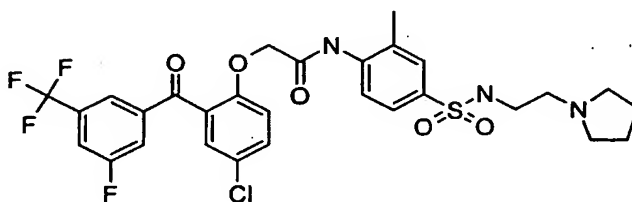
578

Acid 71 was converted to the acid chloride using the general procedure V. Aniline 538 (0.1 g, 0.36 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid

chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford 77 (0.053 g, 23%).

¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.16 (s, 3H), 4 (d, 2H), 4.82 (s, 2H), 7.22-7.31 (m, 2H), 7.55-7.7 (m, 6H), 7.88 (d, 2H), 8.02 (m, 1H), 8.12 (t, 1H), 8.41 (dd, 2H), 9.42 (s, 1H); LC-MS (ES⁺) *m/z* 636 (M+H)⁺, LC-MS (ES⁻) *m/z* 634 (M-H)⁻.

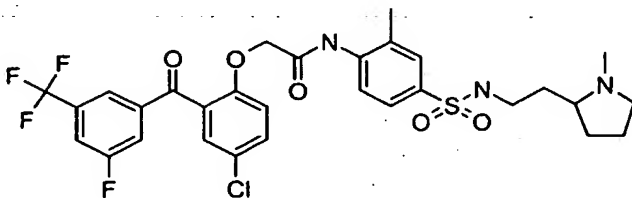
Example 238:



579

Acid 71 was converted to the acid chloride using the general procedure V. Aniline 515 (0.1 g, 0.35 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.4 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford 579 (0.018 g, 8%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.6 (m, 4H), 2.17 (s, 3H), 2.3-2.42 (m, 6H), 2.81 (t, 2H), 3.16 (m, 4H), 4.09 (m, 1H), 4.81 (s, 2H), 7.24 (d, 1H), 7.54-7.69 (m, 5H), 7.88 (d, 2H), 8 (d, 1H), 9.41 (s, 1H); LC-MS (ES⁺) *m/z* 642 (M+H)⁺, LC-MS (ES⁻) *m/z* 640 (M-H)⁻.

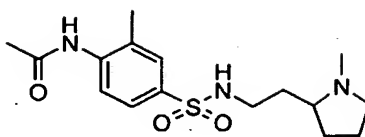
Example 239:



580

Step A:

344

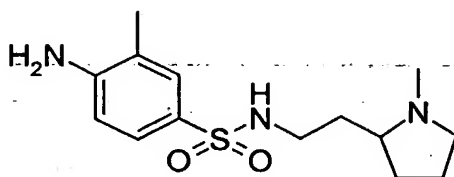


581

Sulfonyl chloride 464 (3 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and 2-(2-aminoethyl)-1-methylpyrrolidine (Aldrich, 0.29 g, 2.3 mmol).

5 The mixture was allowed to stir at rt for 2 d, followed by concentration in vacuo. Water was added to the resulting residue and the mixture was filtered. The filtrate was extracted with dichloromethane and the organic layer was collected, dried over MgSO₄, filtered and concentrated in vacuo to afford the protected sulfonamide 581 (0.40 g, 51%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 1.25 (m, 2H), 1.53 (m, 2H), 1.64 (m, 1H), 1.76 (m, 1H), 1.96 (m, 2H), 2.09 (s, 3H), 2.10 (s, 3H), 2.28 (s, 3H), 2.72 (m, 2H), 2.86 (m, 1H), 7.46 (s, 1H), 7.55 (dd, 1H), 7.59 (s, 1H), 7.76 (d, 1H), 9.42 (s, 1H); LC-MS (ES⁺) *m/z* 340 (M+H)⁺, LC-MS (ES⁻) *m/z* 338 (M-H)⁻.

Step B:



582

The sulfonamide 581 was then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solutions were concentrated in vacuo to afford 582, which was used without further purification.

Step C:

Acid 71 was converted to the acid chloride using the general procedure V. Aniline 582 (0.1 g, 0.34 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by

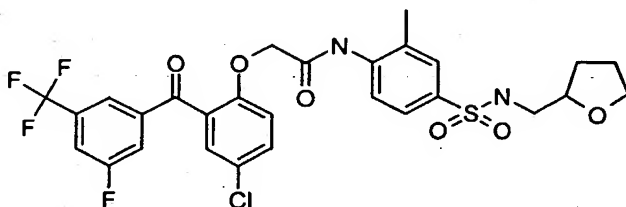
345

flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford **580** (0.037 g, 17%).

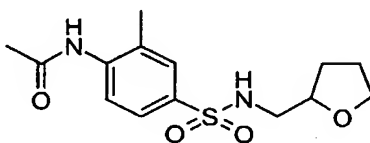
¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.25 (m, 2H), 1.47-1.8 (m, 4H), 1.99 (m, 2H), 2.1 (s, 3H), 2.17 (s, 3H), 2.73 (m, 2H), 2.9 (m, 1H), 4.81 (s, 2H), 7.24 (d, 1H), 7.46-7.69 (m, 6H), 7.88 (m, 2H), 8 (m, 1H), 9.41 (s, 1H); LC-MS (ES⁺) *m/z* 656 (M+H)⁺.

5

Example 240:

**583**

Step A:

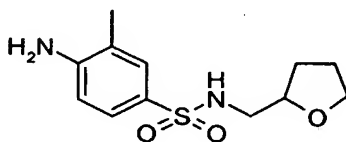
**584**

10

Sulfonyl chloride **464** (3 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and tetrahydrofurfurylamine (Aldrich, 0.41 g, 3.01 mmol). The mixture was allowed to stir at rt for 2 d, followed by concentration in vacuo. Water was added and the mixture was filtered to afford **584** (0.2 g, 64%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 1.45 (m, 1H), 1.7 (m, 3H), 2.05 (s, 3H), 2.23 (s, 3H), 2.69 (t, 2H), 3.51 (m, 1H), 3.62 (m, 1H), 3.72 (m, 1H), 7.5-7.56 (m, 3H), 7.69 (d, 1H), 9.37 (s, 1H); LC-MS (ES⁺) *m/z* 313 (M+H)⁺, LC-MS (ES⁻) *m/z* 311 (M-H)⁻.

15

Step B:

**585**

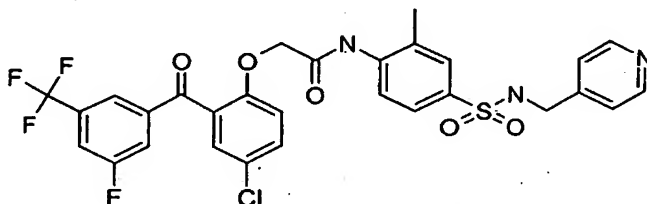
20

Sulfonamide **584** was dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solution was concentrated in vacuo to afford **585**, which was used without further purification.

Step C:

- 5 Acid **71** was converted to the acid chloride using the general procedure V. Aniline **585** (0.1 g, 0.37 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford **583** (0.038 g, 16%).
- 10 ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.69-1.88 (m, 3H), 2.17 (s, 3H), 2.73 (t, 2H), 3.51-3.81 (m, 3H), 4.81 (s, 2H), 7.24 (d, 2H), 7.54-7.69 (m, 6H), 7.88 (m, 2H), 8.01 (m, 1H), 9.41 (s, 1H); LC-MS (AP⁺) *m/z* 629 (M+H)⁺, LC-MS (AP⁻) *m/z* 628 (M-H)⁻.

Example 241:



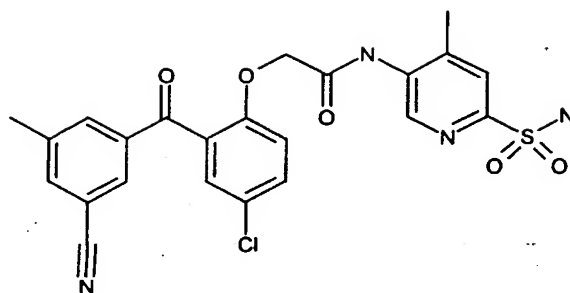
15

586

- Acid **71** was converted to the acid chloride using the general procedure V. Aniline **541** (0.1 g, 0.36 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by
- 20 flash chromatography using 98:2 CH₂Cl₂:CH₃OH as eluant to afford **586** (0.033 g, 14%).
- ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.16 (s, 3H), 4 (d, 2H), 4.82 (s, 2H), 7.24 (m, 3H), 7.55-7.7 (m, 5H), 7.89 (m, 2H), 8.02 (m, 1H), 8.20 (t, 1H), 8.44 (dd, 2H), 9.42 (s, 1H); MS (ES⁺) *m/z* 636 (M+H)⁺.

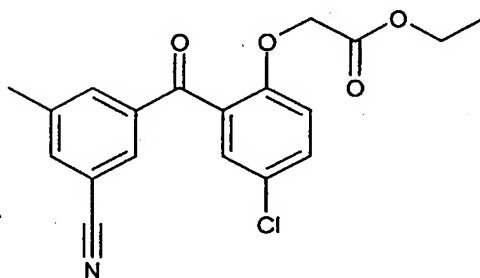
Example 242:

347



587

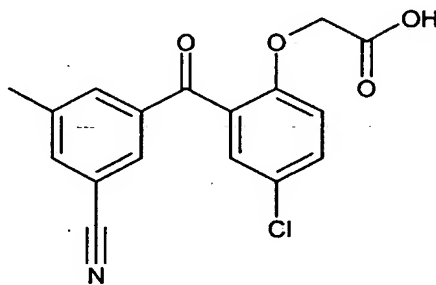
Step A:



588

Compound 568 (2 g, 7.4 mmol), potassium carbonate (5.11 g, 37 mmol), ethyl bromoacetate (1 mL, 9 mmol), and acetone (40 mL) were used as in general procedure II to afford 588 as a yellow/off-white solid (2.73 g, crude material). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 1.14 (t, 3H), 2.39 (s, 3H), 4.08 (m, 2H), 4.78 (s, 2H), 7.14 (d, 1H), 7.47 (d, 1H), 7.58 (d, 1H), 7.9 (m, 3H).

Step B:



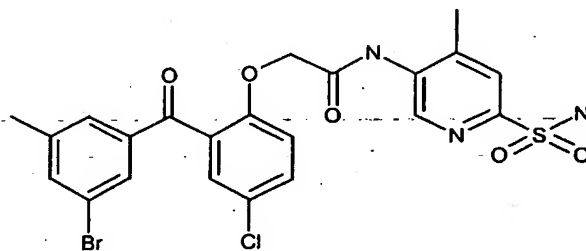
589

Ester **588** (2.73 g, 7.6 mmol), ethanol (EtOH, 20 mL), water (5 mL), and lithium hydroxide monohydrate (0.45 g, 10.7 mmol) were used as in general procedure III to afford **589** as an orange glass (2.45 g, 97%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.3 (s, 3H), 4.67 (s, 2H), 7.1 (d, 1H), 7.44 (d, 1H), 7.58 (dd, 1H), 7.9 (m, 3H), 13.1 (bs, 1H).

Step C:

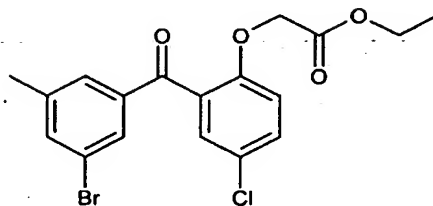
Carboxylic acid **589** (0.1 g, 0.3 mmol), oxalyl chloride (0.4 mL of 2.0 M solution in dichloromethane, 0.8 mmol), DMF (2 drops), and dichloromethane (2 mL), were used according to general procedure V. The acid chloride was dissolved in acetone and added dropwise to aniline **490** (0.086 g, 0.47 mmol), acetone (10 mL), sodium bicarbonate (0.15 g, 1.8 mmol), and water (2 drops) as in general procedure VI. After 4 d, the reaction mixture was concentrated and the product was purified by flash chromatography using 9:1 CH₂Cl₂:CH₃OH as eluant to afford **587** (0.046 g, 31%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.24 (s, 3H), 2.38 (s, 3H), 4.85 (s, 2H), 7.24 (d, 1H), 7.39 (s, 2H), 7.49 (d, 1H), 7.65 (dd, 1H), 7.81 (s, 1H), 7.95 (m, 3H), 8.7 (s, 1H), 9.71 (s, 1H).

Example 243:



590

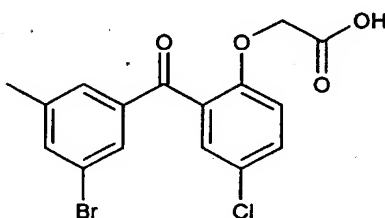
Step A:



591

Compound **570** (0.75 g, 2.3 mmol), potassium carbonate (1.7 g, 12.3 mmol), ethyl bromoacetate (0.3 mL, 2.7 mmol), and acetone (10 mL) were used as in general procedure II to afford **591** as a clear low melting point solid (0.87 g, 92%). The crude product was used without further purification.

5 **Step B:**



592

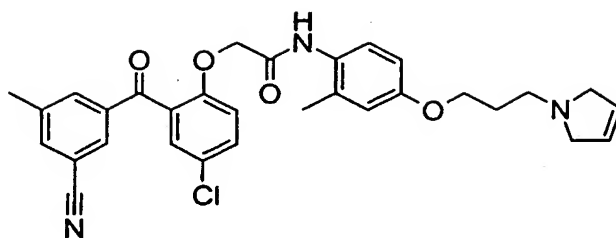
Ester **591** (0.87 g, 2.1 mmol), ethanol (EtOH, 7.5 mL), water (2.5 mL), and lithium hydroxide monohydrate (0.125 g, 2.98 mmol) were used as in general procedure III to afford **592** as a white foam (0.74 g, 91%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.32 (s, 3H), 4.68 (s, 2H), 7.08 (d, 1H), 7.41 (d, 1H), 7.57 (d, 2H), 7.67 (s, 2H), 13.1 (bs, 1H).

Step C:

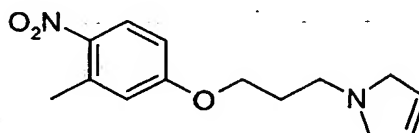
Carboxylic acid **592** (0.1 g, 0.26 mmol), oxalyl chloride (0.4 mL of 2.0 M solution in dichloromethane, 0.8 mmol), DMF (2 drops), and dichloromethane (2 mL), were according to general procedure V. The acid chloride was then dissolved in acetone and added dropwise to aniline **490** (0.086 g, 0.47 mmol), acetone (10 mL), sodium bicarbonate (0.15 g, 1.8 mmol), and water (2 drops) as in general procedure VI. After 5 d, the reaction mixture was concentrated, and the product was purified by flash chromatography using 9:1 CH₂Cl₂:CH₃OH as eluant to afford a solid. The solid was dissolved in dichloromethane, washed with saturated sodium bicarbonate, dried over MgSO₄, filtered, and concentrated in vacuo to give **590** (0.029 g, 20%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.19 (s, 3H), 2.3 (s, 3H), 4.75 (s, 2H), 7.22 (d, 2H), 7.43 (d, 2H), 7.58-7.74 (m, 6H), 8.68 (s, 1H).

Example 244:

350



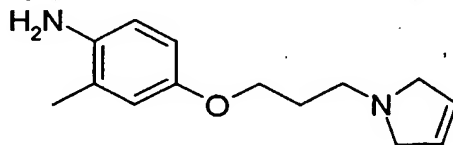
593

Step A:

594

4-(3-bromo-propoxy)-2-methyl-1-nitrobenzene (3.29 g, 12 mmol), DMF (30 mL), and potassium carbonate (7.6 g, 55 mmol) were combined in a round-bottom flask. 3-Pyrroline (Aldrich, 1 g, 14.5 mmol) was added dropwise to the reaction and the resulting solution was stirred at rt overnight. Water was added to the mixture and the resulting mixture was extracted with ethyl acetate. The organic layer was collected, dried over MgSO₄, filtered, and concentrated in vacuo to afford **594** as an orange oil (1.22 g, 39%).

¹H NMR (DMSO-*d*₆; 400 MHz) δ -1.88 (m, 2H), 2.54 (s, 3H), 2.69 (m, 2H), 3.4 (s, 4H), 4.14 (t, 2H), 5.78 (s, 2H), 6.96 (dd, 1H), 7.03 (d, 1H), 8.03 (d, 1H).

Step B:

595

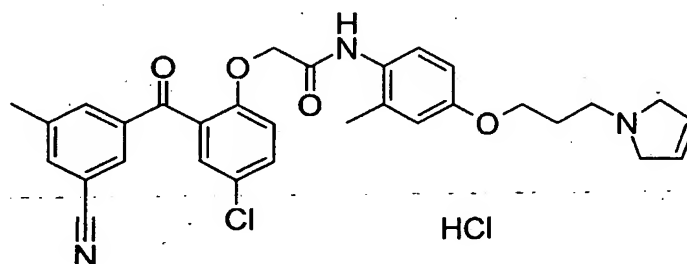
Compound **594** (0.65 g, 2.5 mmol), tin dichloride dihydrate (1.83 g, 8.1 mmol), and ethanol (10 mL) were combined and stirred overnight at rt. Sodium hydroxide (2N) was added and the mixture was extracted with ethyl acetate. The organic layer was collected, washed with water and brine, dried over MgSO₄, filtered, and concentrated in vacuo to afford **595** as a brown oil (0.26 g, 49%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.78 (m, 2H),

2 (s, 3H), 2.65 (m, 2H), 3.37 (s, 4H), 3.83 (t, 2H), 4.34 (bs, 2H), 5.76 (m, 2H), 6.49 (s, 2H), 6.54 (d, 1H).

Step C:

Carboxylic acid **589** (0.2 g, 0.6 mmol), oxalyl chloride (1.4 mL of 2.0 M solution in dichloromethane, 2.8 mmol), DMF (1 drops), and dichloromethane (5 mL), were used to according to general procedure V. The resulting acid chloride was dissolved in acetone and added dropwise to aniline **595** (0.26 g, 1.2 mmol), acetone (10 mL), sodium bicarbonate (0.2 g, 2.4 mmol), and water (1 mL) as in general procedure VI. After 5 d, the reaction mixture was concentrated, and the product was purified by flash chromatography using 95:5 CH₂Cl₂:CH₃OH as eluant to afford **593** as an orange glass (0.127 g, 38%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.86 (m, 4H), 2.01 (s, 3H), 2.36 (s, 3H), 2.76 (m, 2H), 3.48 (m, 2H), 3.97 (t, 2H), 4.7 (s, 2H), 5.8 (s, 2H), 6.7 (m, 2H), 7.12 (d, 1H), 7.22 (d, 1H), 7.48 (d, 1H), 7.65 (dd, 1H), 7.94 (d, 2H), 8.99 (s, 1H).

Example 245:

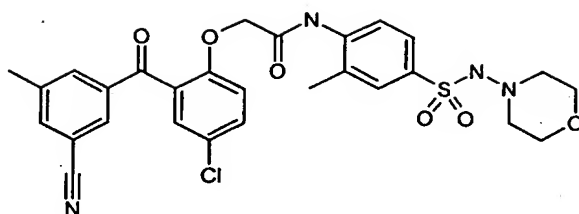


596

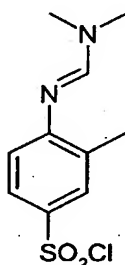
Compound **593** (0.1 g, 0.2 mmol) was dissolved in dioxane (2 mL) and hydrochloric acid (1 mL of a 4M solution in dioxane) was added dropwise. The mixture was allowed to stir for 2 d and was then concentrated in vacuo to afford **596** as a dark solid (0.071 g, 68%). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.02 (s, 5H), 2.36 (s, 3H), 3.68 (m, 2H), 3.95 (m, 4H), 4.2 (m, 2H), 4.71 (s, 2H), 5.93 (s, 2H), 6.75 (m, 2H), 7.2 (m, 2H), 7.49 (d, 1H), 7.65 (d, 1H), 7.95 (m, 3H), 9.06 (s, 1H), 10.95 (bs, 1H).

Example 246:

352

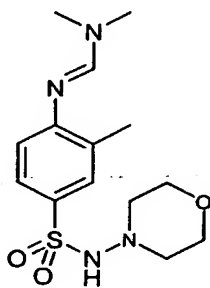


597

Step A:

598

DMF (59 mL, 762 mmol) was added dropwise to stirred solution of oxalyl chloride (380 mL of a 2M solution in dichloromethane, 760 mmol) in a 1-L 3 neck round-bottom flask at 0 °C. After addition was complete, the reaction was stirred for 1 h then allowed to warm to rt and stir for an additional 2 h. To the resulting white solid was added 2-aminotoluene-5-sulfonic acid (Aldrich, 50 g, 267 mmol) in one portion and the resulting reaction mixture was stirred vigorously for an 1 h. The reaction mixture was transferred to a 1-L round-bottom flask and concentrated to afford **598** as tan solid (150.24 g, crude product). The crude product was carried on without further purification or characterization.

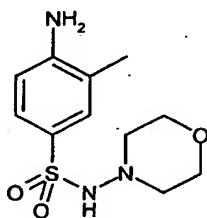
Step B:

599

Compound **598** (10 g, 38 mmol) was added to a solution of 4-aminomorpholine (Aldrich, 5 g, 49 mmol) in THF (40 mL) and stirred at rt for 2 d. Water and saturated sodium

bicarbonate solution were added and the resulting solution was extracted with ethyl acetate. The organic layer was collected, dried over MgSO_4 , filtered, and concentrated in vacuo. The product was further purified by flash chromatography using 95:5 CH_2Cl_2 : CH_3OH as eluant to afford **599** as an orange glass (0.53 g, crude product). The crude product was used without further purification.

Step C:



600

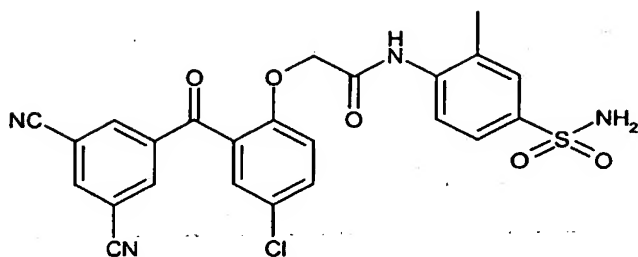
Compound **599** (0.53 g, 1.6 mmol), hydrazine dihydrochloride (0.36 g, 3.4 mmol), and methanol (30 mL) were combined and stirred overnight at rt. The reaction was concentrated in vacuo and the product was purified by flash chromatography using 1:1 hexanes:ethyl acetate as eluant to afford **600** as a white solid (0.075 g, 3.3%). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 2.06 (s, 3H), 2.5 (m, 4H), 3.42 (m, 4H), 5.7 (bs, 2H), 6.62 (d, 1H), 7.34 (m, 2H), 8.23 (s, 1H).

Step D:

Carboxylic acid **589** (0.08 g, 0.24 mmol), oxalyl chloride (0.4 mL of 2.0 M solution in dichloromethane, 0.8 mmol), DMF (1 drops), and dichloromethane (5 mL), were according to general procedure V. The resulting acid chloride was dissolved in acetone and added dropwise to amine **600** (0.07 g, 0.26 mmol), acetone (10 mL), potassium carbonate (0.1 g, 0.72 mmol), and water (1 drop) as in general procedure VI. After 1 d, the reaction mixture was concentrated, suspended in dichloromethane, filtered, then further purified by flash chromatography and TLC prep plate using 98:2 and 95:5 CH_2Cl_2 : CH_3OH as eluant respectively to afford and off-white solid. The resulting solid was further triturated in dichloromethane and filtered to afford **597** as a white solid (0.014 g, 10%). ^1H NMR (CDCl_3 , 300 MHz) δ 2.34 (s, 3H), 2.50 (s, 3H), 2.66 (m, 4H), 3.64 (m, 4H), 4.74 (s, 2H), 5.26 (s, 1H), 7.08 (d, 1H), 7.35 (d, 1H), 7.59 (dd, 1H), 7.72 (s, 1H), 7.85

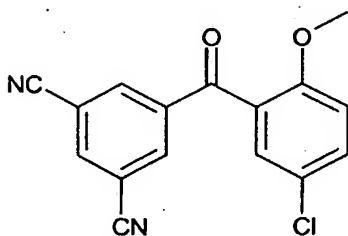
(m, 4H), 8.19 (d, 1H), 8.69 (s, 1H); LC-MS (AP⁺) *m/z* 583 (M+H)⁺, LC-MS (AP⁻) *m/z* 581 (M-H)⁻.

Example 247:



601

Step A:

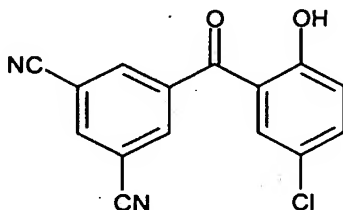


602

Compound 623 (0.5 g, 1.2 mmol), copper (I) cyanide (Aldrich, 0.55 g, 6.1 mmol), pyridine (4 mL, 49.5 mmol), and DMF (15 mL) were combined in a pressure tube equipped with a stir bar, nitrogen on demand, and a reflux condenser. The mixture was allowed to stir at reflux temperature for 4 d. The mixture was cooled, diethyl ether (150 mL) was added, the resulting suspension was filtered through celite and washed with diethyl ether (3 X 150 mL). The filtrate was washed with 2:1 water:concentrated ammonium hydroxide, saturated ammonium chloride, and saturated sodium bicarbonate. The organic layer was collected, dried over MgSO₄, filtered, and concentrated in vacuo. The product was further purified by flash chromatography using 4:1 hexanes:CH₂Cl₂ as eluant to afford 602 as an

off-white solid (0.13 g, 35%). ^1H NMR (DMSO- d_6 , 300 MHz) δ 3.65 (s, 3H), 7.25 (d, 1H), 7.48 (d, 1H), 7.66 (dd, 1H), 8.4 (d, 2H), 8.71 (s, 1H); GC-MS (EI $^+$) m/z 296 (M) $^+$.

Step B:



603

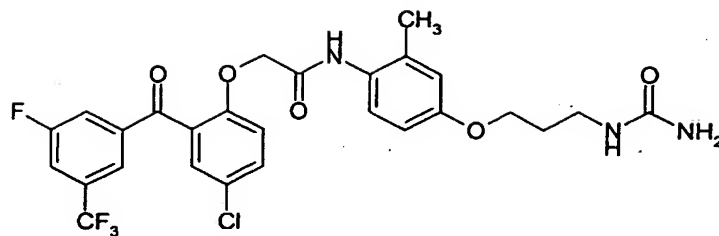
Anisole derivative **602** (0.125 g, 0.42 mmol), dichloromethane (10 mL), and boron tribromide (0.44 mL of a 1 M solution in dichloromethane) were combined as described in general procedure IX. The reaction was stirred at -78°C for 1 h and was then allowed to warm to rt and stir for an additional 1 h. Water (50 mL) was added to the solution and the resulting mixture was stirred vigorously for 15 min, after which time it was added to a separatory funnel. The organic layer was collected, dried over MgSO_4 , filtered, and concentrated in vacuo to give **603** as a yellow glass (0.12 g, 99%). ^1H NMR (DMSO- d_6 , 300 MHz) δ 7 (d, 1H), 7.45 (d, 1H), 7.52 (dd, 1H), 8.42 (d, 2H), 8.7 (m, 1H); GC-MS (EI $^+$) m/z 282 (M) $^+$

Step C:

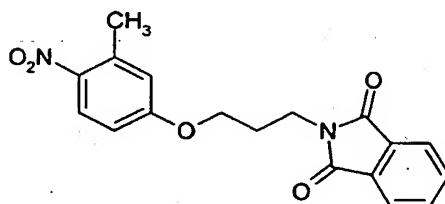
Compound **603** (0.13 g, 0.46 mmol), potassium carbonate (0.12 g, 0.87 mmol), compound **470** (0.146 g, 0.42 mmol), and acetone (5 mL) were combined in a round-bottom flask and stirred at rt overnight. Water (20 mL) was added and the suspension was filtered and the resulting solids were washed with diethyl ether and air dried to afford **601** as an off-white solid (0.212 g, 98%). ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.19 (s, 3H), 4.82 (s, 2H), 7.24 (m, 3H), 7.51-7.74 (m, 3H), 8.5 (d, 2H), 8.69 (m, 1H), 9.5 (s, 1H); LC-MS (AP $^+$) m/z 508 (M+H) $^+$, LC-MS (AP $^-$) m/z 506 (M-H) $^-$.

Example 248:

356

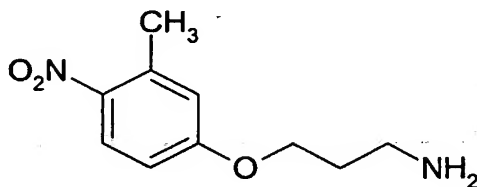


604

Step A:

605

3-Methyl-4-nitrophenol (Aldrich, 5.0 g, 33 mmol), 3-bromopropyl phthalimide (8.8 g, 33 mmol), Cs_2CO_3 (16.1 g, 5.0 mmol), and anhydrous DMF (60 mL) were added to a round bottom flask and heated to 55 °C for 2 h. The reaction was then allowed to cool to rt and was poured into a mixture of Et_2O and water. The resulting solid was filtered, washed with water and Et_2O , and allowed to dry in a vacuum oven at 45 °C for 12-16 h to provide **605** (9.5 g, 85 %) as a tan solid: ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 8.03 (m, 1H), 7.87 (m, 4H), 6.87 (m, 2H), 4.16 (t, 2H), 3.79 (t, 2H), 2.51 (s, 3H), 2.11 (m, 2H).

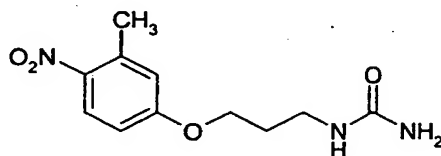
Step B:

606

Into a round bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand were added **605** (3.0 g, 8.8 mmol), hydrazine hydrate (1.6 mL, 1.7 g, 53 mmol),

and absolute ethanol (50 mL). The reaction was heated to reflux and allowed to stir for 4 h, after which time the reaction mixture was allowed to cool to rt and stir for an additional 48-60 h. The resulting heterogenous mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting solid was washed with CH_2Cl_2 , filtered and dissolved in ethyl acetate. The organic layer was washed with water, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to provide **606** (1.1 g, 59%) as a yellow oil: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 7.99 (d, 1H), 6.97 (d, 1H), 6.91 (dd, 1H), 4.10 (t, 2H), 2.63 (t, 2H), 2.49 (s, 3H), 1.77 (m, 2H).

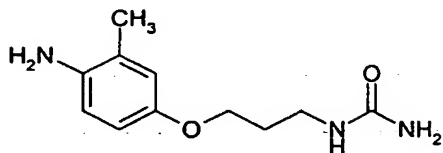
10 **Step C:**



607

Into a round bottom flask equipped with a stir bar and nitrogen on demand were added **606** (0.3 g, 1.43 mmol), anhydrous THF (5 mL), and trimethylsilyl isocyanate (0.21 mL, 0.18 g, 1.57 mmol). The mixture was allowed to stir at rt for 3 h, after which time water (1mL) was added to the heterogeneous solution. The mixture was concentrated under reduced pressure and the resulting residue was washed with a mixture of ethyl acetate and Et_2O , filtered, and dried to afford **607** (0.273 g, 75%) as a pale yellow solid: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 8.00 (d, 1H), 6.97 (d, 1H), 6.90 (dd, 1H), 5.97 (t, 1H), 5.35 (bs, 2H), 4.04 (t, 2H), 3.05 (m, 2H), 2.44 (s, 3H), 1.77 (m, 2H).

Step D:



608

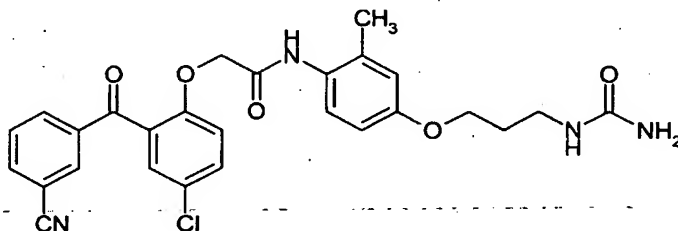
To a flask equipped with a stir bar were added **607** (0.055 g, 0.22 mmol), ethanol (8 mL), and palladium on carbon (0.006 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 40 p.s.i. When judged to be complete, the reaction mixture was filtered through celite and the solvents were removed under reduced pressure

to provide 608 (0.045 g, 92%) as a white solid: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 6.51 (s, 1H), 6.46 (m, 2H), 5.92 (t, 1H), 5.33 (bs, 2H), 4.30 (bs, 2H), 3.75 (t, 2H), 3.03 (m, 2H), 1.96 (s, 3H), 1.67 (m, 2H).

Step E:

- 5 Acid 71 (0.17 g, 0.45 mmol), oxalyl chloride (0.25 mL of a 2 M solution in CH_2Cl_2 , 0.50 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline 608 (0.95 g, 0.43 mmol), NaHCO_3 (0.19 g, 2.3 mmol), acetone (5 mL), and water (1 mL) were used according to general procedure VI. The resulting solid was washed with Et_2O , filtered, and dried in
10 vacuo at 50 °C to afford 604 (0.115 g mg, 44 %) as a white solid: MS (ES+) m/z 581 (M^+); ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 9.10 (s, 1H), 8.01 (d, 1H), 7.86 (m, 2H), 7.67 (dd, 1H), 7.54 (d, 1H), 7.22 (d, 1H), 7.08 (d, 1H), 6.75 (d, 1H), 6.69 (dd, 1H), 5.98 (t, 1H), 5.37 (bs, 2H), 4.70 (s, 2H), 3.91 (t, 2H), 3.08 (q, 2H), 1.99 (s, 3H), 1.76 (m, 2H).

15 **Example 249:**



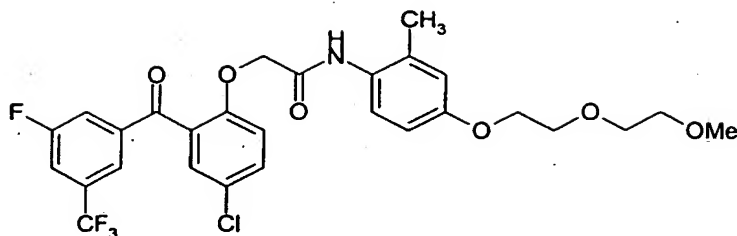
609

Step A:

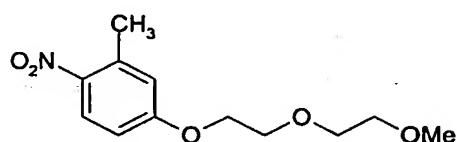
- 20 Acid 129 (0.14 g, 0.45 mmol), oxalyl chloride (0.25 mL of a 2 M solution in CH_2Cl_2 , 0.50 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline 608 (0.095 g, 0.43 mmol), NaHCO_3 (0.19 g, 2.3 mmol), acetone (5 mL), and water (1 mL) were used according to general procedure VI. The resulting residue was treated with Et_2O and a solid precipitated. The solid was purified by flash chromatography using 5% MeOH: CH_2Cl_2 to afford 609 (0.015 g, 6%) as a white solid: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 9.01 (s, 1H), 8.13 (s, 1H), 8.03 (m, 2H), 7.63 (m, 2H), 7.47 (d, 1H), 7.18 (d, 1H), 7.07 (d, 1H), 6.72 (d, 1H), 6.65 (dd, 1H), 5.94 (m, 1H), 5.34 (bs, 2H), 4.65 (s, 2H), 3.87 (t, 2H), 3.03 (m, 2H), 1.95 (s, 3H), 1.76 (m, 2H).

Example 250:

359

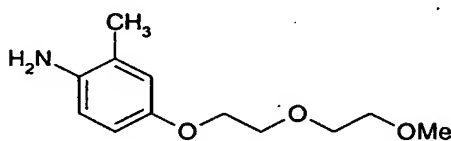


610

Step A:

611

To a round bottom flask equipped with a stir bar and nitrogen on demand were added 5-fluoro-2-nitrotoluene (1.0 g, 6.45 mmol), di(ethylene glycol) methyl ether (0.77 mL, 0.77 g, 6.45 mmol), anhydrous DMF (20 mL), and K_2CO_3 (1.8 g, 12.9 mmol). The reaction mixture was heated to 80 °C and allowed to stir for 16-18 h, after which time additional di(ethylene glycol) methyl ether (1.15 mL, 1.16 g, 9.67 mmol) was added. The reaction was heated to 130 °C and allowed to stir for 16-18 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into ethyl acetate and water. The organic layer was washed with 5% NaOH aqueous solution, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **611** (1.07 g, 65%) as a yellow oil: 1H NMR (DMSO- d_6 , 300 MHz) δ 8.06 (d, 1H), 7.08 (d, 1H), 7.01 (dd, 1H), 4.24 (t, 2H), 3.78 (t, 2H), 3.60 (m, 2H), 3.48 (m, 2H), 3.27 (s, 3H), 2.57 (s, 3H).

Step B:

612

To a flask equipped with a stir bar were added **611** (0.36 g, 1.4 mmol), ethanol (10 mL), and palladium on charcoal (0.036 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 43 p.s.i for 2 h, after which time the reaction mixture was filtered through celite. To the filtrate were added 1N HCl and ethyl acetate. The layers were separated and the pH of the aqueous layer was adjusted using saturated $NaHCO_3$.

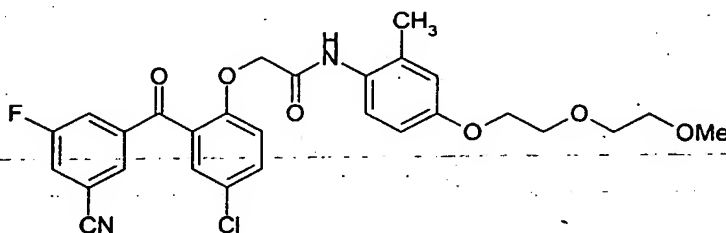
The aqueous layer was extracted with ethyl acetate, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to provide **612** (0.18 g, 57%) as a yellow oil: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 6.52 (s, 1H), 6.46 (s, 1H), 4.32 (bs, 2H), 3.86 (t, 2H), 3.60 (m, 2H), 3.50 (m, 2H), 3.39 (m, 2H), 3.19 (s, 3H), 1.96 (s, 3H).

5 **Step C:**

Acid **71** (0.16 g, 0.42 mmol), oxalyl chloride (0.04 mL, 0.058 g, 0.46 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline **612** (0.09 g, 0.40 mmol), NaHCO_3 (0.176 g, 2.1 mmol), acetone (7 mL), and water (1 mL) were used according to general
10 procedure VI. The resulting residue was treated with diethyl ether to afford **610** (0.061 g, 25%) as a white solid: MS (ES+) m/z 584 (M^+); ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 9.06 (s, 1H), 7.97 (d, 1H), 7.82 (m, 2H), 7.63 (dd, 1H), 7.49 (d, 1H), 7.18 (d, 1H), 7.05 (d, 1H), 6.73 (s, 1H), 6.66 (dd, 1H), 4.66 (s, 2H), 3.98 (t, 2H), 3.65 (t, 2H), 3.52 (m, 2H), 3.40 (m, 2H), 3.19 (s, 3H), 1.95 (s, 3H).

15

Example 251:



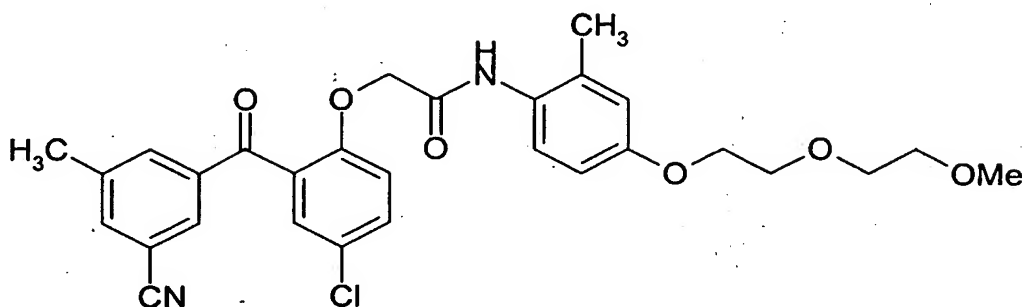
613

Step A:

20 Acid **496** (0.1 g, 0.3 mmol), oxalyl chloride (0.03 mL, 0.042 g, 0.33 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline **612** (0.065 g, 0.29 mmol), NaHCO_3 (0.126 g, 1.5 mmol), acetone (10mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 2%
25 MeOH: CH_2Cl_2 as eluant and then rechromatographed using 1:1 hexanes:ethyl acetate as eluant. Upon standing, crystals formed in the collected fractions. The crystals were collected and dried to afford **613** (0.012 g, 7 %) a pink crystalline solid: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 9.08 (s, 1H), 8.09 (d, 1H), 7.99 (s, 1H), 7.87 (d, 1H), 7.63 (dd, 1H), 7.48

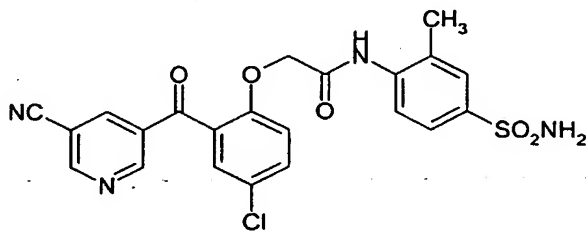
361

(d, 1H), 7.17 (d, 1H), 7.08 (d, 1H), 6.74 (d, 1H), 6.67 (dd, 1H), 4.67 (s, 2H), 3.99 (t, 2H), 3.65 (t, 2H), 3.51 (m, 2H), 3.40 (m, 2H), 3.19 (s, 3H), 1.95 (s, 3H).

Example 252:

614

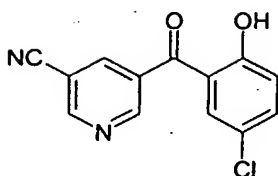
Acid 589 (0.138 g, 0.42 mmol), oxalyl chloride (0.04 mL, 0.058 g, 0.46 mmol), N, N-dimethylformamide (1 drop), and CH₂Cl₂ (7 mL) were used according to general procedure V. The resulting acid chloride, aniline 612 (0.09 g, 0.40 mmol), NaHCO₃ (0.176 g, 2.1 mmol), acetone (7 mL), and water (1 mL) were used according to general procedure VI. The product was purified by flash chromatography using 1:1 hexanes: ethyl acetate as eluant and subsequently treated with Et₂O to afford 614 (0.048 g, 21%) as a beige solid: MS (ES⁺) *m/z* 537 (M⁺); ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.95 (s, 1H), 7.92 (s, 1H), 7.86 (m, 2H), 7.61 (dd, 1H), 7.45 (d, 1H), 7.18 (d, 1H), 7.08 (d, 1H), 6.74 (s, 1H), 6.67 (m, 1H), 4.66 (s, 2H), 3.99 (t, 2H), 3.65 (t, 2H), 3.51 (q, 2H), 3.40 (q, 2H), 3.19 (s, 3H), 2.31 (s, 3H), 1.96 (s, 3H).

Example 253:

615

20 Step A:

362

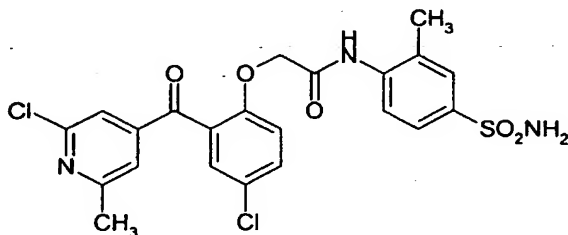


616

To a round bottom flask equipped with a reflux condenser, stir bar, and nitrogen on demand were placed **44** (0.45 g, 1.44 mmol), copper (I) cyanide (0.32 g, 3.6 mmol), and anhydrous DMF (20 mL). The reaction mixture was heated to reflux and allowed to stir for 3 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into ethyl acetate and water. The resulting emulsion was filtered, the organic layer was collected, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford **616** (0.2 g, 54%) as a yellow solid: ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.59 (s, 1H), 9.17 (d, 1H), 9.00 (d, 1H), 8.54 (m, 1H), 7.48 (dd, 1H), 7.43 (d, 1H), 6.95 (d, 1H).

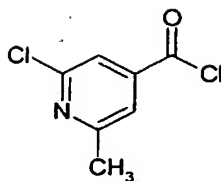
Step B:

A mixture of **616** (0.20 g, 0.77 mmol), **470** (0.237 g, 0.77 mmol), potassium carbonate (0.213 g, 1.5 mmol), and sodium iodide (230 mg, 1.54 mmol) in 8 mL of acetone was warmed to reflux for 6 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The residue was treated with Et₂O and the resulting solid was filtered and recrystallized from CH₃CN to provide **615** (8 mg, 3%): ¹H NMR (DMSO-*d*₆, 300 MHz) δ 9.48 (s, 1H), 9.20 (d, 1H), 9.13 (d, 2H), 8.64 (t, 1H), 7.64 (m, 5H), 7.25 (m, 3H), 4.81 (s, 2H), 2.17 (s, 3H).

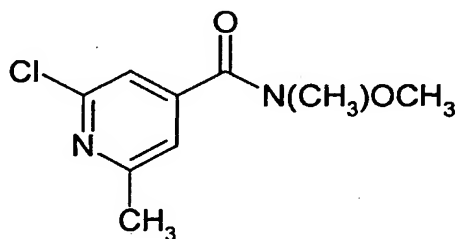
Example 254:

617

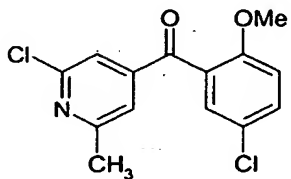
363

Step A:**618**

2-Chloro-6-methylisonicotinic acid (1 g, 5.8 mmol), CH₂Cl₂ (20 mL), oxalyl chloride (0.56 mL, 0.8 g, 6.4 mmol), and N,N-dimethylformamide (1 drop) were used according to general procedure V to afford **618** (1.1 g, >99%) as a purple oil. The product was used in the next step without further purification.

Step B:**619**

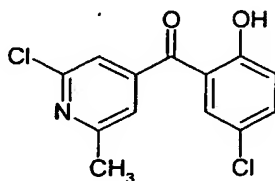
Acid chloride **618** (1.1 g, 5.8 mmol), N,O-dimethylhydroxylamine hydrochloride (1.1 g, 11.6 mmol), Et₃N (1.6 mL, 1.2 g, 11.6 mmol), and CHCl₃ (50 mL) were used according to general procedure VII to provide **619** (1.3 g, >99%) as a purple oil. The product was used in the next step without further purification: ¹H NMR (DMSO-*d*₆, 300 MHz) δ 7.42 (s, 1H), 7.38 (s, 1H), 3.54 (s, 3H), 3.24 (s, 3H).

Step C:**620**

Amide **619** (1.3 g, 5.8 mmol), n-butyllithium (4 mL of a 1.6 M solution in hexanes, 6.4 mmol), 2-bromo-4-chloroanisole (0.8 mL, 1.3 g, 5.8 mmol), and diethyl ether (25 mL) were used according to general procedure VIII. The product was purified by flash chromatography using 3:2 hexanes:ethyl acetate as eluant to afford **620** (0.2 g, 12%) as a

pale yellow solid: ^1H NMR (DMSO- d_6 , 300 MHz) δ 7.67 (dd, 1H), 7.50 (d, 1H), 7.42 (s, 1H), 7.38 (s, 1H), 7.24 (d, 1H), 3.65 (s, 3H), 2.51 (s, 3H).

Step D:



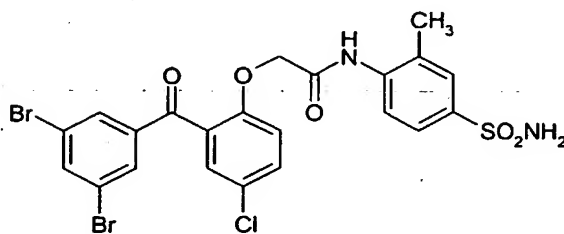
621

Anisole **620** (0.2 g, 0.68 mmol), BBr_3 (1.4 mL of a 1.0 M solution in CH_2Cl_2 , 1.4 mmol), and CH_2Cl_2 (5 mL) were used according to general procedure IX to afford **621** (0.163 g, 85%) as a yellow solid. The product was used without further purification: ^1H NMR (DMSO- d_6 , 400 MHz) δ 10.56 (s, 1H), 7.47 (dd, 1H), 7.41 (s, 1H), 7.38 (m, 2H), 6.93 (d, 1H), 2.47 (s, 3H).

Step E:

A mixture of **621** (0.08 g, 0.28 mmol), **470** (0.086 g, 0.28 mmol), and potassium carbonate (0.077 g, 0.56 mmol) in 10 mL of acetone was warmed to reflux for 1.5 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. The residue was treated with MeOH and the resulting solid was filtered to provide **617** (0.007 g, 5%): MS (ES+) m/z 508 (M^+); ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.38 (s, 1H), 7.64 (m, 1H), 7.61 (s, 1H), 7.56 (s, 2H), 7.50 (m, 2H), 7.45 (s, 1H), 7.20 (m, 3H), 4.75 (s, 2H), 2.42 (s, 3H), 2.13 (s, 3H).

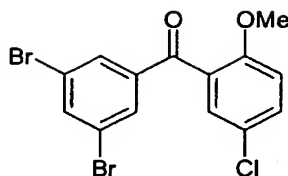
Example 255:



622

Step A:

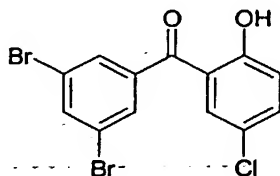
365



623

A solution of 1,3,5-tribromobenzene (3.0 g, 9.53 mmol) in 50 mL of ether was cooled to –78 °C in a dry ice/acetone bath. *n*-Butyllithium (4.2 mL of a 2.5 M solution in hexanes, 10.5 mmol) was added dropwise over 10 min. The resulting mixture was stirred at –78 °C for an additional 10 min, then 183 (2.0 g, 9.53 mmol) was added in small portions over 10 min. The reaction mixture was lifted from the cold bath, allowed to warm to rt and continue stirring for 1.5 h. The mixture was poured into water and extracted with Et₂O. The organic layers were collected, dried over MgSO₄, filtered, and concentrated *in vacuo*.

The resulting orange residue was treated with MeOH, filtered and dried to provide 623 (2.03 g, 53%) as a yellow solid: ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.12 (m, 1H), 7.71 (m, 2H), 7.60 (dd, 1H), 7.43 (d, 1H), 7.20 (d, 1H), 3.63 (s, 3H).

Step B:

624

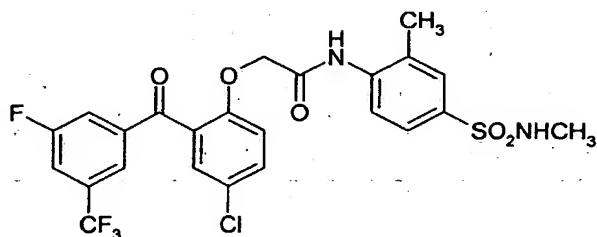
Anisole 623 (0.2 g, 0.49 mmol), BBr₃ (1 mL of a 1.0 M solution in CH₂Cl₂, 1 mmol), and CH₂Cl₂ (8 mL) were used according to general procedure IX to afford 624 (0.176 g, 92%) as a yellow solid. The product was used without further purification: ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.46 (s, 1H), 8.10 (m, 1H), 7.74 (m, 2H), 7.43 (dd, 1H), 7.35 (d, 1H), 6.93 (d, 1H).

Step C:

A mixture of 624 (0.12 g, 0.31 mmol), 470 (0.095 g, 0.31 mmol), potassium carbonate (0.086 g, 0.62 mmol), sodium iodide (0.093 g, 0.62 mmol) and 10 mL of acetone were warmed to reflux for 12-16 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The residue

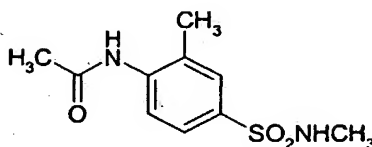
was treated with Et₂O and the resulting solid was filtered and dried to provide **622** (0.04 g, 21%) as a yellow solid: ¹H NMR (DMSO-*d*₆, 00 MHz) δ 9.35 (s, 1H), 8.07 (t, 1H), 7.83 (m, 2H), 7.60 (m, 4H), 7.47 (d, 1H), 7.20 (m, 3H), 4.77 (s, 2H), 2.14 (s, 3H).

Example 256:



625

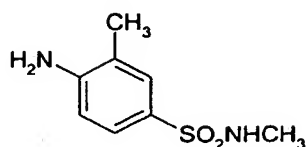
Step A:



626

Into a round bottom flask equipped with a stir bar and gas dispersion tube was added sulfonyl chloride **464** (11.5 g, 0.046 mol) and THF (250 mL) and the mixture was cooled to 0 °C. Methylamine gas was bubbled through the reaction mixture for 0.5 h, after which time, the mixture was poured into EtOAc and water. The pH of the aqueous layer was adjusted to 7 using concentrated HCl. The organic layer was collected, dried over MgSO₄, filtered and the solvents were removed under reduced pressure. The resulting orange residue was treated with Et₂O, filtered and dried to provide **626** (5.32 g, 48%): ¹H NMR (DMSO-*d*₆, 300 MHz) δ 9.46 (s, 1H), 7.80 (d, 1H), 7.58 (m, 2H), 7.34 (m, 1H), 2.41 (d, 3H), 2.32 (s, 3H), 2.13 (s, 3H).

Step B:

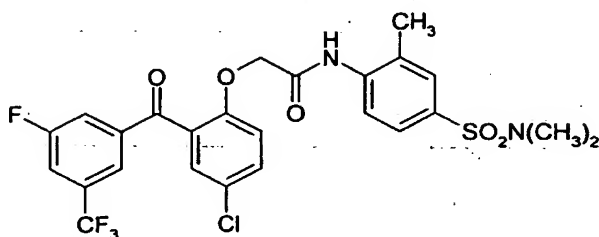
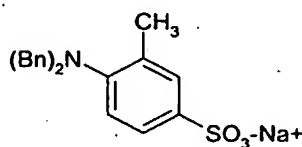


627

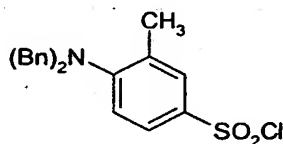
Into a round bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand were placed **626** (6.2 g, 0.026 mol), ethanol (250 mL), and 1.5 N (75 mL). The mixture was warmed to reflux and allowed to stir for 6 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into a cold solution of saturated NaHCO₃. The mixture was extracted with several portions of EtOAc and the organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to provide **627** (3.6 g, 69%) as a yellow solid: ¹H NMR (DMSO-*d*₆, 400 MHz) δ 7.23 (m, 2H), 6.82 (m, 1H), 6.59 (d, 1H), 5.62 (bs, 2H), 2.26 (d, 3H), 2.03 (s, 3H).

Step C:

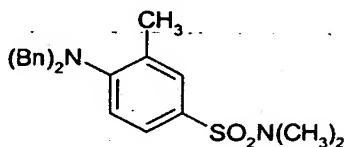
Acid **71** (0.237 g, 0.63 mmol), oxalyl chloride (0.35 mL of a 2 M solution in CH₂Cl₂, 0.69 mmol), N, N-dimethylformamide (1 drop), and CH₂Cl₂ (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **627** (0.12 g, 0.60 mmol), NaHCO₃ (0.264 g, 3.2 mmol), acetone (7 mL), and water (1 mL) were used according to general procedure VI. The resulting residue was treated with Et₂O and filtered to afford **625** (0.158 g, 45%) as a white solid: MS (ES+) *m/z* 558 (M⁺); ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.38 (s, 1H), 7.97 (d, 1H), 7.84 (m, 2H), 7.62 (m, 2H), 7.55 (m, 1H), 7.50 (m, 2H), 7.30 (m, 1H), 7.19 (d, 1H), 4.77 (s, 2H), 2.34 (d, 3H), 2.13 (s, 3H).

Example 257:**628****Step A:****629**

Into a round bottom flask equipped with a stir bar, reflux condenser and nitrogen on demand was added 2-aminotoluene-5-sulfonic acid (10 g, 0.053 mol), CH_2Cl_2 (120 mL), Na_2CO_3 (22.3 g, 0.21 mol) as a solution in water (120 mL), and the benzyl bromide (14.3 mL, 20.5 g, 0.12 mol). The reaction mixture was warmed to reflux and allowed to stir for 72 h. When judged to be complete, EtOH was added to the reaction mixture and the solvents were removed under reduced pressure to afford **629** (27.4 g, >100%) as a brown oil. The product was used in the next step without further purification.

Step B:**630**

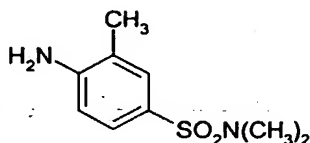
Into a round bottom flask equipped with a stir bar and nitrogen on demand were added **629** (20.6 g, 0.053 mol) and anhydrous DMF (200 mL). The mixture was cooled to 0 °C and thionyl chloride (11.7 mL, 19.0 g, 0.16 mol) was added dropwise over 15 min, after which time the reaction mixture was allowed to warm to rt and stir for an additional 2 h. When judged to be complete, the mixture was poured into ice water and was allowed to stir for 30 min. The aqueous mixture was extracted with EtOAc and the organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford **630** (5.0 g, 24%). The product was used without further purification.

Step C:**631**

Dimethylamine (11.6 mL of a 5.6 M solution in EtOH, 0.065 mol) was placed in a round bottom flask equipped with a stir bar and nitrogen on demand, and cooled to 0 °C. Sulfonyl chloride **630** (5.0 g, 0.013 mol) was added portion-wise over 10 min and the reaction mixture was allowed to stir at 0 °C for 30 min. When judged to be complete, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was collected, dried over MgSO_4 , filtered and concentrated under reduced pressure. The

product was filtered through a pad of silica gel using CH_2Cl_2 as eluant and the filtrate concentrated under reduced pressure to afford **631** (1.0 g, 20%) as a yellow oil: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 7.47 (d, 1H), 7.22 (m, 11H), 7.05 (d, 1H), 4.13 (s, 4H), 2.48 (s, 6H), 2.44 (s, 3H).

5

Step D:**632**

10

To a plastic-coated reaction vessel equipped with a stir bar, was added **631** (0.330 g, 0.85 mmol), toluene (10 mL), and palladium on charcoal (50 mg of 10% by weight Pd/C). The vessel was placed on a hydrogenation apparatus at 40 p.s.i. When the reaction was judged to be complete, it was filtered through celite and the filtrate was washed with saturated NaHCO_3 and water. The organic layer was collected, dried over MgSO_4 , filtered and the solvents were removed under reduced pressure to provide **632** (120 mg, 67%) as a beige solid: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 7.19 (m, 2H), 6.64 (d, 1H), 5.74 (bs, 2H), 2.44 (s, 6H), 2.04 (s, 3H).

15

Step E:

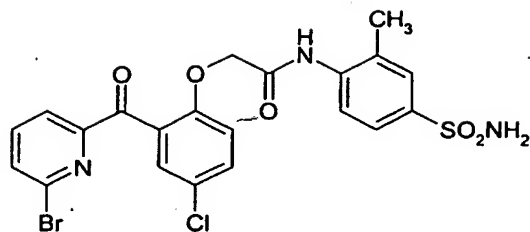
20

Acid **71** (0.222 g, 0.59 mmol), oxalyl chloride (0.32 mL of a 2 M solution in CH_2Cl_2 , 0.65 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid-chloride, aniline **632** (0.12 g, 0.56 mmol), NaHCO_3 (248 mg, 3.0 mmol), acetone (7 mL), and water (1 mL) were used according to general procedure VI. The resulting residue was treated with Et_2O and filtered to afford **628** (0.142 g, 42%) as a white solid: MS (ES+) m/z 572 (M^+); ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 9.37 (s, 1H), 7.96 (d, 1H), 7.83 (m, 2H), 7.73 (d, 1H), 7.62 (dd, 1H), 7.50 (m, 3H), 7.19 (d, 1H), 4.78 (s, 2H), 2.53 (s, 6H), 2.17 (s, 3H).

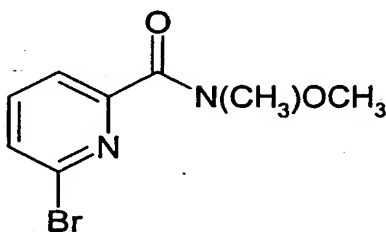
25

Example 258:

370

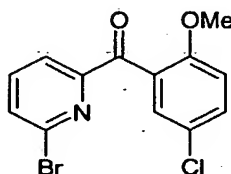


633

Step A:

634

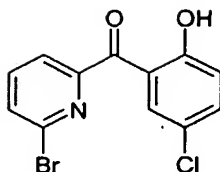
Picolinic acid (3 g, 0.015 mol), CH_2Cl_2 (50 mL), oxalyl chloride (1.5 mL, 2.2 g, 0.017 mol), and N,N-dimethylformamide (4-5 drops) were used according to general procedure V. The resulting acid chloride, N,O-dimethylhydroxylamine hydrochloride (2.9 g, 0.03 mol), Et_3N (4.2 mL, 3.0 g, 0.03 mol), and CHCl_3 (50 mL) were used according to general procedure VII to provide **634** (3.7 g, >99%) as a yellow oil. The product was used without further purification: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 7.83 (m, 1H), 7.72 (m, 1H), 7.59 (d, 1H), 3.61 (s, 3H), 3.21 (s, 3H).

Step B:

635

Amide **634** (3.7 g, 0.015 mol), n-butyllithium (6.4 mL of a 2.5 M solution in hexanes, 0.016 mol), 2-bromo-4-chloroanisole (2.1 mL, 3.3 g, 0.015 mol), and anhydrous diethyl ether (20 mL) were used according to general procedure VIII. The product was purified by flash chromatography using 9:1 hexanes:ethyl acetate as eluant and subsequently recrystallized from MeOH to afford **635** (2.25 g, 46%) as a white solid: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 7.90 (m, 3H), 7.55 (dd, 1H), 7.44 (d, 1H), 7.17 (d, 1H), 3.58 (s, 3H).

371

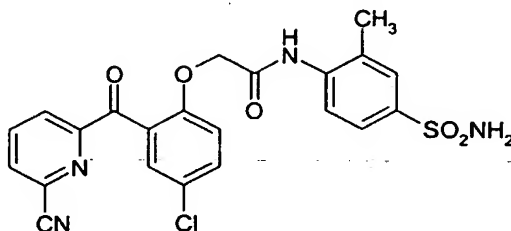
Step C:**636**

- 5 Anisole **635** (0.227 g, 0.85 mmol), BBr_3 (1.7 mL of a 1.0 M solution in CH_2Cl_2 , 1.7 mmol), and CH_2Cl_2 (15 mL) were used according to general procedure IX to afford **636** (0.069 g, 26%) as a yellow solid. The product was used in the next step without further purification: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 10.40 (s, 1H), 7.88 (m, 3H), 7.43 (m, 2H), 6.99 (d, 1H).

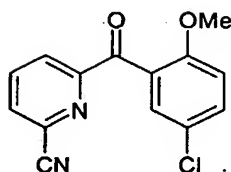
10 **Step D:**

- A mixture of **636** (0.07 g, 0.22 mmol), **482** (0.081 g, 0.23 mmol), potassium carbonate (0.061 g, 0.44 mmol) in 10 mL of acetone was heated to reflux. When the reaction was judged to be complete, it was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. The resulting solid was washed with warm CH_3CN , filtered and dried to provide **633** (0.027 g, 23%) as a white solid: MS (ES+) m/z 540 (M+H); ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 9.23 (s, 1H), 7.88 (m, 3H), 7.56 (m, 5H), 7.23 (m, 3H), 4.66 (s, 2H), 2.09 (s, 3H).

20 **Example 259:**

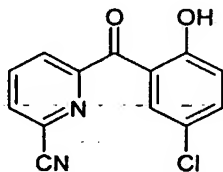
**637****Step A:**

372



638

Into a round bottom flask equipped with a stir bar, nitrogen on demand, and a reflux condenser were added 635 (0.750 g, 2.3 mmol), sodium cyanide (0.225 g, 4.6 mmol),
 5 copper (I) iodide (0.078 g, 0.41 mmol), and acetonitrile (10 mL). A stream of nitrogen was bubbled through the reaction mixture for 5 min, after which time tetrakis-
 (triphenylphosphine)palladium (1.0 g, 0.89 mmol) was added and the mixture was heated to reflux for 2 h. The reaction mixture was allowed to cool to rt and poured into EtOAc and water. The organic layer was collected, dried over MgSO₄, filtered, and concentrated
 10 under reduced pressure. The orange residue was treated with Et₂O and the resulting solid was filtered and dried to provide 638 (321 mg, 51%) as a pale yellow solid: ¹H NMR (DMSO-*d*₆, 300 MHz) δ 8.23 (m, 3H), 7.63 (dd, 1H), 7.51 (d, 1H), 7.22 (d, 1H), 3.59 (s, 3H).

Step B:

639

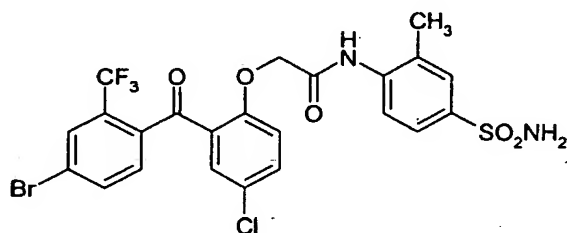
15 Anisole 638 (0.32 g, 1.17 mmol), BBr₃ (2.3 mL of a 1.0 M solution in CH₂Cl₂, 2.3 mmol), and CH₂Cl₂ (15 mL) were used according to general procedure IX. The resulting residue was recrystallized from MeOH to afford 639 (0.046 g, 15%) as an orange solid: ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.39 (s, 1H), 8.20 (m, 3H), 7.45 (m, 2H), 6.90 (d, 1H).
 20

Step C:

A mixture of 639 (0.045 g, 0.17 mmol), 482 (0.064 g, 0.18 mmol), potassium carbonate (0.047 g, 0.34 mmol) in 10 mL of acetone was heated to reflux. When the reaction was judged to be complete, the mixture was allowed to cool to rt and was poured
 25 into EtOAc and water. The organic layer was collected, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The resulting solid was recrystallized

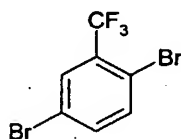
from CH₃CN, filtered and dried to provide 637 (19 mg, 23%) as a pale yellow solid: MS (ES) *m/z* 484 (M⁺), 483 (M-H)⁻; ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.31 (s, 1H), 8.20 (m, 3H), 7.57 (m, 5H), 7.20 (m, 3H), 4.64 (s, 2H), 2.10 (s, 3H).

5 **Example 260:**



640

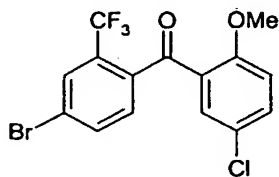
Step A:



641

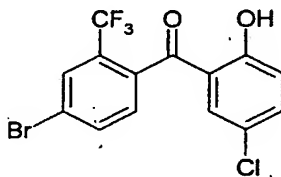
To a round bottom flask equipped with a stir bar and nitrogen on demand were added copper (II) bromide (5.36 g, 0.024 mol) and CH₃CN (100 mL). The reaction mixture was cooled to 0 °C and *t*-butyl nitrite (3.8 mL, 3.3 g, 0.032 mol) was added dropwise over 15 min. 2-amino-5-bromobenzotrifluoride (5 g, 0.021 mol) was added dropwise over 15 min and the resulting mixture was allowed to continue stirring at 0 °C for 1.5 h. The mixture was then allowed to warm to RT and stir for an additional 16-18 h. When judged to be complete, the mixture was concentrated to ½ the original volume, was poured into 1N HCl and extracted with Et₂O. The organic layer was collected and concentrated under reduced pressure to afford 641 (5.5 g, 86 %) as a yellow oil: ¹H NMR (DMSO-*d*₆, 400 MHz) δ 7.96 (s, 1H), 7.78 (m, 2H).

Step B:



642

A solution of **641** (5.5 g, 18 mmol) in 60 mL of ether was cooled to -78°C in a dry ice/acetone bath. *n*-Butyllithium (9.2 mL of 2.5 M solution in hexanes, 23 mmol) was added dropwise over 10 min. The resulting mixture was stirred at -78°C for an additional 10 min, then **183** (3.8 g, 18 mmol) was added in small portions over 10 min. The reaction mixture was allowed to warm to rt and continue stirring for 2 h and was poured into water and extracted with EtOAc. The organic layer was collected, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The product was purified by flash chromatography using 2% EtOAc in hexanes as eluant to provide **642** (1.7 g, 24%) as a yellow oil: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 8.03 (d, 1H), 7.88 (m, 1H), 7.65 (dd, 1H), 7.60 (d, 1H), 7.36 (d, 1H), 7.16 (d, 1H), 3.47 (s, 3H).

Step C:**643**

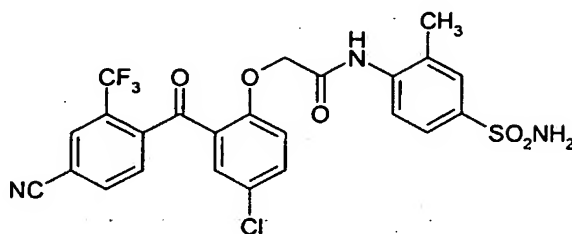
Anisole **642** (0.5 g, 1.27 mmol), BBr_3 (2.5 mL of a 1.0 M solution in CH_2Cl_2 , 2.5 mmol), and CH_2Cl_2 (10 mL) were used according to general procedure IX to afford **643** (0.4 g, 83%) as a yellow oil. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 10.71 (s, 1H), 8.03 (s, 1H), 7.92 (d, 1H), 7.50 (m, 3H), 6.90 (d, 1H).

Step D:

A mixture of **643** (0.400 g, 1.05 mmol), **470** (0.322 g, 1.05 mmol), potassium carbonate (0.290 g, 2.1 mmol) and sodium iodide (0.315 g, 2.1 mmol) in 15 mL of acetone was warmed to reflux and allowed to stir for 16 h. When the reaction was judged to be complete, the mixture was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. The resulting residue was purified by flash chromatography using 3% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as eluant to provide a yellow solid. The solid was recrystallized from CH_3CN , filtered and dried to provide **640** (16 mg, 3%) as a white

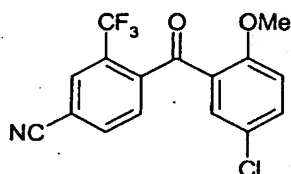
solid: ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.31 (s, 1H), 8.01 (s, 1H), 7.90 (d, 2H), 7.66 (m, 5H), 7.47 (d, 1H), 7.24 (m, 3H), 4.67 (s, 2H), 2.23 (s, 3H).

Example 261:



644

Step A:

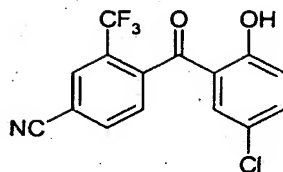


645

- 10 Into a round bottom flask equipped with a stir bar, nitrogen on demand, and a reflux condenser were added **642** (0.250 g, 0.64 mmol), sodium cyanide (0.063 g, 1.3 mmol), copper (I) iodide (0.023 g, 0.12 mmol), and acetonitrile (10 mL). A stream of nitrogen was bubbled through the reaction mixture for 5 min., after which time tetrakis-
- 15 (triphenylphosphine)palladium (0.086 g, 0.08 mmol) was added and the mixture was heated to reflux for 6 h. The reaction mixture was allowed to cool to rt and resulting precipitate was filtered. The precipitate was dissolved in EtOAc and washed with water. The organic layer was collected, filtered through a pad of celite, dried over MgSO_4 , filtered, and concentrated under reduced pressure to provide an orange residue. The residue was treated with Et_2O , filtered and dried to afford **645** (57 mg, 26%) as a white
- 20 solid: ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.27 (s, 1H), 8.16 (d, 1H), 7.71 (dd, 1H), 7.64 (d, 1H), 7.56 (d, 1H), 7.22 (d, 1H), 3.54 (s, 3H).

Step B:

376

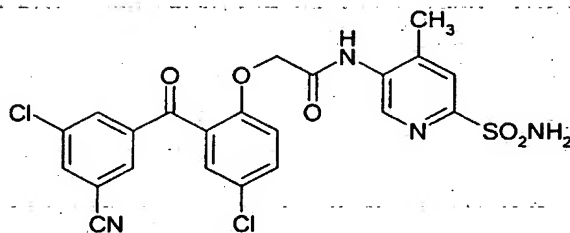


646

Anisole **645** (0.126 g, 0.37 mmol), BBr_3 (0.74 mL of a 1.0 M solution in CH_2Cl_2 , 0.74 mmol), and CH_2Cl_2 (15 mL) were used according to general procedure IX. The resulting
 5 residue was treated with Et_2O and filtered to afford **646** (0.077 g, 64%) as a pale yellow solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 10.80 (s, 1H), 8.25 (s, 1H), 8.16 (d, 1H), 7.64 (d, 1H), 7.55 (dd, 1H), 7.45 (d, 1H), 6.95 (d, 1H).

Step C:

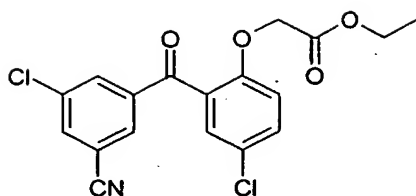
A mixture of **646** (0.077 g, 0.24 mmol), **482** (0.089 g, 0.25 mmol), potassium carbonate (0.066 g, 0.48 mmol) in 10 mL of acetone was heated to reflux. When the reaction was judged to be complete, it was allowed to cool to rt and was poured into
 15 EtOAc and water. The organic layer was collected, dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. The resulting residue was treated with Et_2O to provide a yellow solid. The solid was recrystallized from CH_3CN , filtered and dried to provide **644** (11 mg, 3%) as a pale yellow solid: ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 9.31 (s, 1H), 8.18 (s, 1H), 8.05 (d, 1H), 7.64 (m, 6H), 7.23 (m, 3H), 4.69 (s, 2H), 2.17 (s, 3H).

Example 262:

647

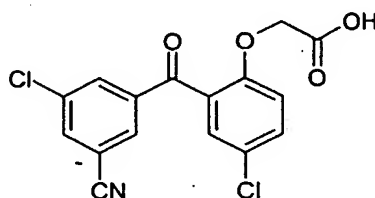
Step A:

377



648

Phenol 477 (0.345 g, 1.2 mmol), K_2CO_3 (0.326 g, 2.4 mmol), ethyl bromoacetate (0.14 mL, 0.207 g, 1.3 mmol) and acetone (10 mL) were used according to general procedure II to provide 648 as an orange oil (0.46 g, >99%). The product was without further purification: 1H NMR (DMSO- d_6 , 400 MHz) δ 8.28 (t, 1H), 8.04 (d, 1H), 7.98 (t, 1H), 7.58 (dd, 1H), 7.47 (d, 1H), 7.11 (d, 1H), 4.73 (s, 2H), 4.07 (m, 2H), 1.11 (m, 3H).

Step B:

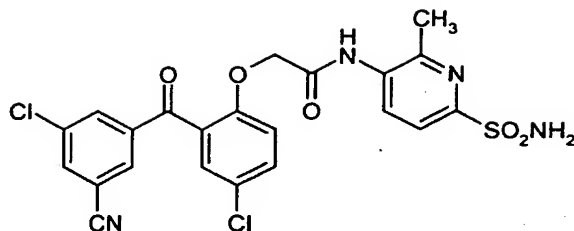
649

Ester 648 (0.46 g, 1.2 mmol), THF (4 mL), water (1 mL), EtOH (1 mL) and LiOH (0.128 g, 3.1 mmol) were used according to general procedure III to afford 649 (0.25 g, 60 %) as a yellow foam. The product was used without further purification: 1H NMR (DMSO- d_6 , 400 MHz) δ 13.1 (bs, 1H), 8.27 (s, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 7.57 (dd, 1H), 7.45 (d, 1H), 7.08 (d, 1H), 4.63 (s, 2H), 4.07 (m, 2H), 1.11 (m, 3H).

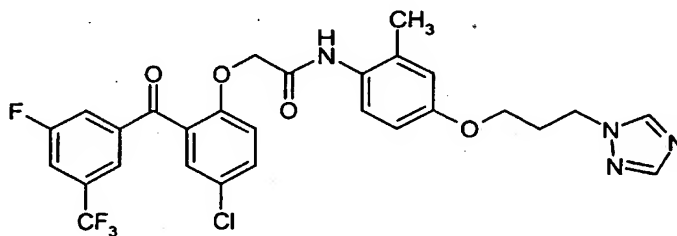
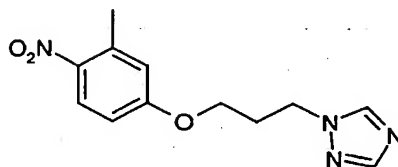
Step C:

Acid 649 (0.120 g, 0.34 mmol), oxalyl chloride (0.04 mL, 0.06 g, 0.48 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline 490 (0.064 g, 0.34 mmol), $NaHCO_3$ (0.14 g, 1.7 mmol), acetone (7 mL), and water (1 mL) were used according to general procedure VI. The resulting residue purified by flash chromatography using 3% MeOH: CH_2Cl_2 as eluant to afford 647 (0.01 g, 6 %) as a pale yellow solid: MS (ES+) m/z 519 (M^+): 1H NMR (400 MHz, DMSO- d_6) δ 9.72 (s, 1H), 8.66 (s, 1H), 8.26 (s, 1H), 8.12 (s, 1H), 8.04 (s, 1H), 7.75 (d, 1H), 7.62 (dd, 1H), 7.50 (d, 1H), 7.34 (s, 2H), 7.20 (d, 1H), 4.81 (s, 2H), 2.20 (s, 3H) ppm.

378

Example 263:**650**

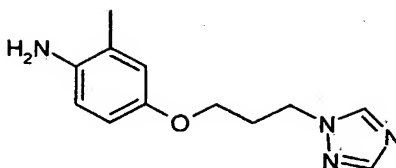
Acid **649** (0.1g, 0.3 mmol) was converted to the acid chloride by general procedure V, and
 5 coupled with 5-amino-6-methyl-2-pyridinesulfonamide (0.06g, 0.33 mmol, 1.1 eq.) as
 outlined in Step E for the synthesis of compound **503** in example 206 to give **650**. LCMS
 (ES⁺) 520 m+1/z. ¹H NMR (DMSO-*d*₆) δ 9.65 (br s, 1H, NH), 8.3 (s, 1H, Ar), 8.1 (m,
 2H, Ar), 8.0 (s, 1H, Ar), 7.7 (d, 1H, Ar), 7.6 (dd, 1H, Ar), 7.5 (d, 1H, Ar), 7.32 (bs, 2H,
 NH₂), 7.2 (d, 1H, Ar), 4.8 (s, 2H, CH₂), 2.3 (s, 3H, CH₃).

Example 264:**651****Step A:****652**

4-(3-Bromo-propoxy)-2-methyl-1-nitrobenzene (1 g, 3.6 mmol) and 1,2,4-triazole
 (Aldrich, 0.25 g, 3.6 mmol) were used in the same manner as to prepare compound 139.
 Compound **652** (0.45 g, 48%) was obtained as an oil. ¹H NMR (DMSO-*d*₆, 400 MHz) δ
 2.4 (br s, 4H), 2.45 (s, 3H), 4.1 (t, 2H), 6.9 (dd, 1H), 6.92 (d, 1H), 7.9 (d, 2H), 8 (d, 1H).

Step B:

379

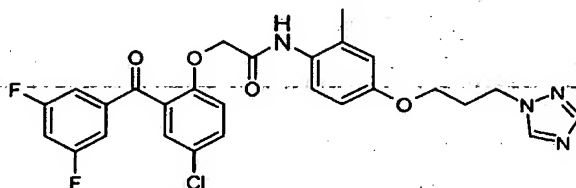


653

Compound 652 was used in the same manner as that to prepare compound 140. Aniline 653 was obtained as an oil (0.33 g, 84%). The compound was used without further purification.

Step C:

Acid 71 (0.26 g, 0.7 mmol), oxalyl chloride (0.09 mL, 1 mmol), DMF (1 drop), and CH_2Cl_2 were used according to general procedure V to afford the desired acid chloride. The acid chloride, aniline 653 (0.16 g, 0.7 mmol), NaHCO_3 (0.3 g, 3 mmol), acetone (8 mL), and water (0.3 mL) were used according to general procedure VI. Flash column chromatography of the crude product on silica gel with 2% methanol in CH_2Cl_2 afforded 651 (0.05 g, 12%) as a white solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 1.9 (s, 3H), 2.1-2.2 (m, 2H), 3.8 (t, 2H), 4.3 (t, 2H), 4.66 (s, 2H), 6.6 (dd, 1H), 6.7 (d, 1H), 7.03 (d, 1H), 7.2 (d, 1H), 7.5 (d, 1H), 7.6 (dd, 1H), 7.8-7.82 (m, 2H), 7.9 (s, 1H), 8 (d, 1H), 8.5 (s, 1H), 9.02 (s, 1H).

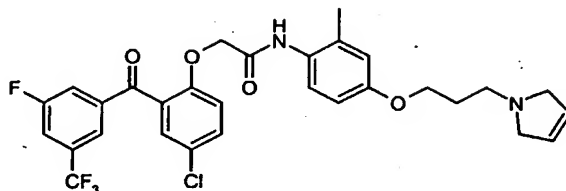
Example 265:

654

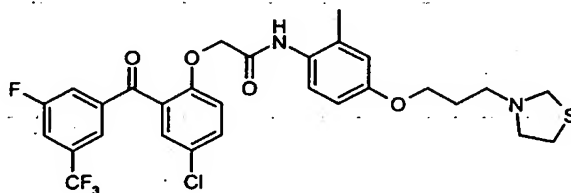
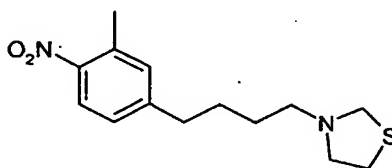
Acid 49 (0.14 g, 0.4 mmol), oxalyl chloride (0.2 mL, 2 mmol), DMF (1 drop), and CH_2Cl_2 were used according to general procedure V. The resulting acid chloride, aniline 653 (0.1 g, 0.4 mmol), NaHCO_3 (0.17 g, 1.7 mmol), acetone (5 mL), and water (0.1 mL) were used according to general procedure VI. Flash column chromatography of the crude product on silica gel with 2% methanol in CH_2Cl_2 resulted in 654 (0.04 g, 18%) as a white solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 1.9 (s, 3H), 2.1-2.2 (m, 2H), 3.8 (t, 2H), 4.3 (t, 2H), 4.7 (s,

380

2H), 6.6 (dd, 1H), 6.7 (d, 1H), 7.08 (d, 1H), 7.2 (d, 1H), 7.3-7.4 (m, 2H), 7.42-7.6 (m, 3H), 7.9 (s, 1H), 8.5 (s, 1H), 9 (s, 1H).

Example 266:**655**

Acid **71** (1.4 g, 3.6 mmol), thionyl chloride (1.3 mL, 18 mmol), DMF (1 drop), and CH_2Cl_2 were used according to general procedure V to afford the desired acid chloride. The acid chloride, aniline **595** (0.84 g, 3.6 mmol), NaHCO_3 (1.36 g, 16 mmol), acetone (50 mL), and water (1 mL) were used according to general procedure VI. Flash column chromatography of the crude product on silica gel with 5% methanol in CH_2Cl_2 afforded **655** (0.53 g, 25%) as a solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 1.7-1.8 (m, 2H), 1.95 (s, 3H), 2.6-2.7 (m, 2H), 3.4 (br s, 4H), 3.9 (t, 2H), 4.66 (s, 2H), 5.7 (s, 2H), 6.6 (dd, 1H), 6.7 (d, 1H), 7.0 (d, 1H), 7.2 (d, 1H), 7.5 (d, 1H), 7.6 (dd, 1H), 7.8-7.82 (m, 2H), 8 (d, 1H), 9.02 (s, 1H).

Example 267:**656****Step A:****657**

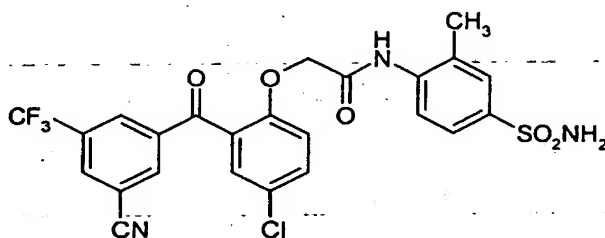
4-(3-Bromo-propoxy)-2-methyl-1-nitrobenzene (1 g, 3.6 mmol) and thiazolidine (Aldrich, 0.34 mL, 4.3 mmol) were used in the same manner as to prepare compound 139.

Compound 657 (0.45 g, 48%) was obtained as an oil and was used without further purification.

5 **Step B:**

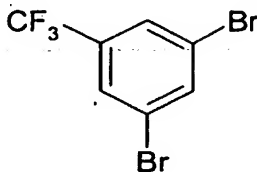
The nitro group of 657 (1 g, 3.5 mmol) was reduced under catalytic conditions (H_2 , 10% Pd/C in EtOH). Acid 71 (1.3 g, 3.5 mmol), thionyl chloride (1.3 mL, 18 mmol), DMF (1 drop), and CH_2Cl_2 were used according to general procedure V to afford the desired acid chloride. The resultant crude aniline, acid chloride, $NaHCO_3$ (1.4 g, 16 mmol), acetone
10 (50 mL), and water (1 mL) were used according to general procedure VI. Flash column chromatography of the crude product on silica gel with EtOAc:hexane (7:3) resulted in 656 (0.14 g, 7%) as a white solid. 1H NMR ($DMSO-d_6$, 300 MHz) δ 1.7-1.8 (m, 2H), 2 (s, 3H), 2.4 (t, 2H), 2.8 (t, 2H), 3 (t, 2H), 3.9-4 (m, 5H), 4.7 (s, 1H), 6.6 (dd, 1H), 6.7 (d, 1H), 7.0 (d, 1H), 7.2 (d, 1H), 7.5 (d, 1H), 7.6 (dd, 1H), 7.8-7.82 (m, 2H), 8 (d, 1H), 9.02 (s,
15 1H).

Example 268:



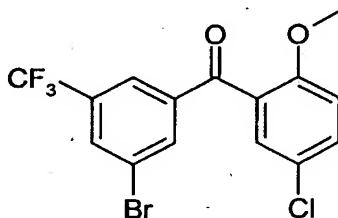
20 **658**

Step A:

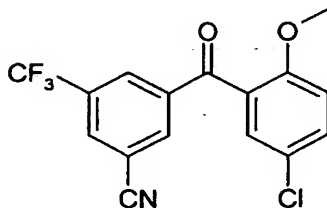


25 **659**

To a solution of copper (II) bromide (5.36 g, 24 mmol) in acetonitrile (100 ml) at 0 °C was added t-butyl nitrite (3.8 ml, 32 mmol) dropwise, and then 3-amino-5-bromobenzotrifluoride (5 g, 21 mmol) dropwise. The mixture was stirred at 0 °C for 1.5 h, then at room temperature for 16 h. The mixture was then concentrated to half of its original volume in vacuo, and then poured into 1N HCl (120 ml). This mixture was extracted with ether (100 mL). The organic layer was washed with 1N HCl, dried (Na₂SO₄), filtered, concentrated in vacuo (Note: product is fairly volatile, and should not be exposed to high vacuum for extended periods of time) to give **659** as a brown oil (5.12 g), which was used as is without further purification. ¹H NMR (CDCl₃, 400MHz) δ 7.82 (s, 1H), 7.67 (s, 2H).

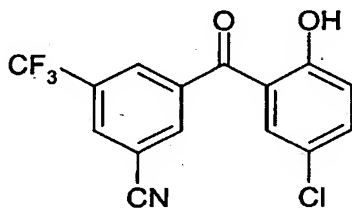
Section B:**660**

659 (5.12 g), *N*-methyl-*N*-methoxy-2-methoxy-5-chlorobenzamide (3.6 g, 16.8 mmol), and *n*-butyllithium (8.76 ml of 2.7M solution in heptane) were treated according to the procedure outlined in Part A of Example 2 to give **660** (3.36 g), which was used as is without further purification. ¹H NMR (CDCl₃, 400MHz) δ 8.02 (s, 1H), 7.89 (d, 2H), 7.46 (dd, 1H), 7.38 (d, 1H), 6.92 (d, 1H), 3.66 (s, 3H).

Section C:**661**

660 (3.36 g, 8.55 mmol), sodium cyanide (838 mg, 17 mmol), copper (I) iodide (325 mg, 1.7 mmol), and tetrakis(triphenylphosphine)palladium (0) (987 mg, 0.86 mmol) were used according to General Procedure A to give **661** (1.35 g) after silica gel purification (10% ethyl acetate/hexanes). ¹H NMR (CDCl₃, 400MHz) δ 8.19 (s, 1H), 8.13 (s, 1H), 8.04 (s, 1H), 7.50 (dd, 1H), 7.43 (d, 1H), 6.94 (1H), 3.65 (s, 3H).

Section D:



662

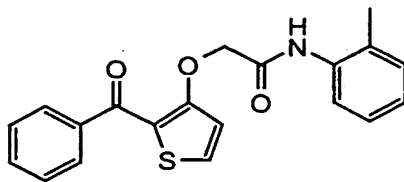
- 661** (1.35 g, 3.98 mmol) was treated according to the procedure for the synthesis of compound **4** to give **662** (1.29 g, >99%) as a yellow oil, which was used without further purification. ¹H NMR (CDCl₃, 300MHz) δ 11.49 (s, 1H), 8.20-8.16 (m, 3H), 7.59 (dd, 1H), 7.38 (d, 1H), 7.15 (d, 1H).

Step E:

- 662** (487 mg, 1.5 mmol) and **470** were treated according to **Step D** in **Example 197** to give a crude product which was purified by silica gel chromatography (8:1:1 CH₂Cl₂/ethyl acetate/methanol) and triturated with ether to give **658** (315 mg) as an off-white solid. ¹H NMR (DMSO-d₆, 400MHz) δ 9.41 (s, 1H), 8.56 (s, 1H), 8.45 (s, 1H), 8.27 (s, 1H), 7.66-7.52 (m, 5H), 7.19 (m, 3H), 4.76 (s, 2H), 2.12 (s, 3H); MS(ES⁻): *m/z* 550 (M-H).

20

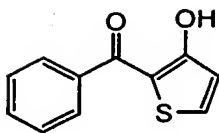
Example 269:



663

Step A:

384

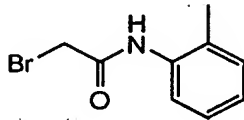


664

A mixture of 3-methoxythiophene (1.14 g, 10 mmol), aluminum chloride (2.67 g, 20 mmol), and benzoyl chloride (1.16 mL, 10 mmol) in 50 mL of methylene chloride was heated to reflux for 20 h. The reaction mixture was then poured over ice and stirred at room temperature for 5 h, after which the aqueous layer was separated and extracted with 20 mL of CH₂Cl₂. The combined organic layers were then dried over MgSO₄, filtered and concentrated *in vacuo* to give 1.897 g of orange oil. Purification by flash chromatography using 5-7% EtOAc/hexane as eluant gave 664 (0.823 g, 40%) as a yellow crystalline solid:

¹H NMR (CDCl₃, 400 MHz) δ 12.35 (s, 1 H), 7.92 (dd, 2 H), 7.56-7.46 (m, 4 H), 6.83 (d, 1 H).

Step B:



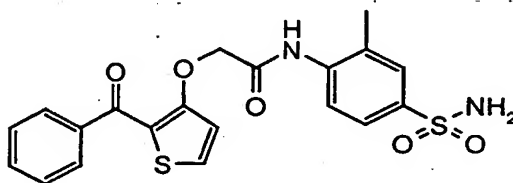
665

A solution of *o*-toluidine (2.67 mL, 25 mol) and pyridine (2.2 mL, 27.5 mmol) in 200 mL of chloroform was cooled to 0 °C in an ice bath. Bromoacetyl bromide (2.4 mL, 27.5 mmol) was added dropwise over 7 min, and the resulting mixture was allowed to slowly warm to rt and stirred for 24 h. The reaction mixture was then poured into 150 mL of water. The aqueous layer was separated and extracted with 100 mL of CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo* to give 665 (5.86 g, quantitative): ¹H NMR (CDCl₃, 400 MHz) δ 8.10 (br s, 1 H), 7.81 (d, 1H), 7.20-7.17 (m, 2 H), 7.10-7.06 (m, 1 H), 4.04 (s, 2 H), 2.27 (s, 3 H).

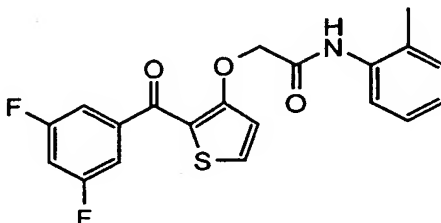
Step C:

A mixture of 664 (0.204 g, 1.0 mmol), 665 (0.235 g, 1.03 mmol), and potassium carbonate (0.622 g, 4.5 mmol) in 10 mL of acetone was warmed to reflux for 6 h, then stirred at room temperature an additional 16 h. The reaction mixture was then poured into 30 mL of

water and extracted with two 30-mL portions of EtOAc. The combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo* to yield 0.448 g of crude material. Purification by flash chromatography using 35% EtOAc/hexanes as the eluant gave **663** (0.272 g, 77%): MS (ES+) m/z 352 (M+H); ^1H NMR (CDCl_3 , 400 MHz) δ 8.53 (br s, 1 H), 7.81-7.79 (m, 2 H), 7.59 (d, 1 H), 7.42-7.38 (m, 3 H), 7.19-7.16 (m, 2 H), 7.10-7.07 (m, 1 H), 6.93 (d, 1 H), 4.73 (s, 2 H), 2.19 (s, 3 H).

Example 270:**666**

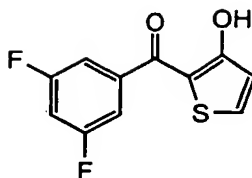
A mixture of **664** (0.218 g, 1.07 mmol), **470** (0.338 g, 1.1 mmol), and potassium carbonate (0.622 g, 4.5 mmol) in 10 mL of acetone was warmed to reflux for 5 h. The reaction mixture was then poured into 30 mL of water and extracted with 30 mL of EtOAc. The pH of the aqueous layer was adjusted to 7 using 3 M HCl, then extracted with 30 mL of EtOAc. The combined organic layers were filtered to remove yellow solid, dried over MgSO_4 , filtered, and concentrated *in vacuo* to give 0.360 g of crude material. This material was suspended in CH_2Cl_2 and acetone and filtered, then suspended in MeOH and filtered to give **666** (0.076 g, 17%): MS (ES+) m/z 431 (M+H); ^1H NMR (CDCl_3 , 400 MHz) δ 9.29 (s, 1 H), 7.96 (d, 1 H), 7.77 (d, 2 H), 7.67 (d, 1 H), 7.62 (d, 1 H), 7.58 (dd, 1 H), 7.50 (t, 1 H), 7.43-7.48 (m, 2 H), 7.23 (br s, 2 H), 7.15 (d, 1 H), 4.83 (s, 2 H), 2.16 (s, 3 H).

Example 271:

386

667

Step A:



668

- 5 A mixture of 3-methoxythiophene (1.14 g, 10 mmol), aluminum chloride (2.70 g, 20.2 mmol), and 3,5-difluorobenzoyl chloride (1.18 mL, 10 mmol) in 50 mL of methylene chloride was heated to reflux for 20 h, then stirred at room temperature for 27 h. The reaction mixture was then poured over ice and stirred at room temperature for 40 min, after which the aqueous layer was separated and extracted with 20 mL of CH₂Cl₂. The
10 combined organic layers were then dried over MgSO₄, filtered and concentrated *in vacuo* to give 1.214 g of brown solid. Purification by flash chromatography using 2% EtOAc/hexane as eluant gave 668 (0.518 g, 22%) as a yellow solid: ¹H NMR (CDCl₃, 400 MHz) δ 12.04 (s, 1 H), 7.57 (d, 1 H), 7.43 (dd, 2 H), 7.02-6.97 (m, 1 H), 6.84 (d, 1 H).

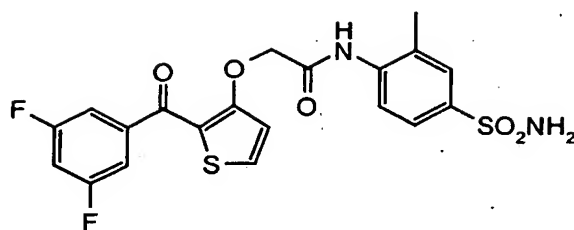
15 Step B:

- A mixture of 668 (0.192 g, 0.80 mmol), 665 (0.188 g, 0.82 mmol), and potassium carbonate (0.498 g, 3.6 mmol) in 10 mL of acetone was warmed to reflux for 6 h. The reaction mixture was then poured into 30 mL of water and extracted with two 30-mL portions of EtOAc. The combined organic layers were dried over MgSO₄, filtered, and
20 concentrated *in vacuo* to give crude material. Purification by flash chromatography using 35-40% EtOAc/hexane as eluant gave 667 as a yellow solid (0.069 g, 22%): MS (ES+) *m/z* 388 (M+H); ¹H NMR (CDCl₃, 400 MHz) δ 8.75 (br s, 1 H), 7.74 (d, 1 H), 7.66 (d, 1 H), 7.36-7.32 (m, 2 H), 7.23-7.21 (m, 2 H), 7.15-7.10 (m, 1 H), 6.99 (d, 1 H), 6.96-6.89 (m, 1 H), 4.80 (s, 2 H), 2.32 (s, 3 H).

25

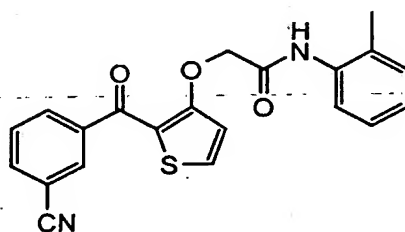
Example 272:

387



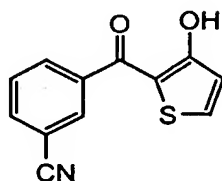
669

A mixture of 668 (0.192 g, 0.80 mmol), 470 (0.252 g, 0.82 mmol), and potassium carbonate (0.498 g, 3.6 mmol) in 10 mL of acetone was warmed to reflux for 6 h. The reaction mixture was then poured into 30 mL of water and extracted with two 30-mL portions of EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo* to give 0.272 g of crude material. Purification by flash chromatography using 35-50% EtOAc/hexane as eluant gave 669 as a yellow solid (0.103 g, 28%): MS (ES+) *m/z* 467 (M+H); ¹H NMR (CDCl₃, 400 MHz) δ 9.47 (br s, 1 H), 8.06 (d, 1 H), 7.72-7.52 (m, 3 H), 7.50-7.40 (m, 3 H), 7.26 (br s, 2 H), 7.17 (d, 1 H), 4.89 (s, 2 H), 2.23 (s, 3 H).

Example 273:

670

Step A:



671

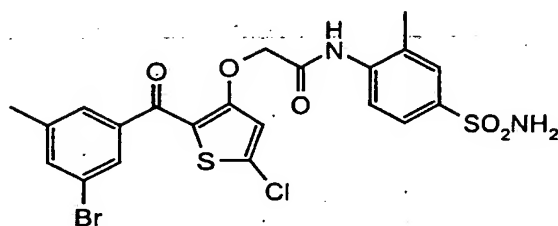
A mixture of 3-methoxythiophene (1.14 g, 10 mmol), aluminum chloride (2.78 g, 20.8 mmol), and 284 (10 mmol) in 50 mL of methylene chloride was heated to reflux for 24 h, then stirred at room temperature for 15 h. The reaction mixture was then poured over ice

and stirred at room temperature for 1 h, after which the aqueous layer was separated and extracted with 35 mL of CH_2Cl_2 . The combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo* to give 2.239 g of brown oil. Purification by flash chromatography using 5% EtOAc/hexane as eluant gave **671** (0.195 g, 9%): ^1H NMR (400 MHz, CDCl_3) δ 12.04 (s, 1 H), 8.19 (s, 1 H), 8.13 (d, 1 H), 7.83 (d, 1 H), 7.64-7.58 (m, 2 H), 6.86 (d, 1 H).

Step B:

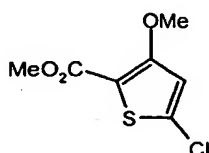
A mixture of **671** (0.164 g, 0.72 mmol), **665** (0.168 g, 0.74 mmol), and potassium carbonate (0.448 g, 3.24 mmol) in 12 mL of acetone was warmed to reflux for 15 h, then stirred at room temperature for an additional 5.5 h. Since the reaction mixture went dry overnight, another 10 mL of acetone was added, and the mixture was heated to reflux for 6 h, then stirred at room temperature overnight. The reaction mixture was poured into 50 mL of water and extracted with two 35-mL portions of EtOAc. The combined organic layers were dried over MgSO_4 , filtered, and concentrated *in vacuo* to give 1.251 g of brown oil. Purification by flash chromatography using 30-40% EtOAc/hexane as eluant gave **670** as a yellow solid (0.033g, 12%): MS (ES+) m/z 377 (M+H); ^1H NMR (CDCl_3 , 400 MHz) δ 8.63 (br s, 1 H), 8.07 (s, 1 H), 8.01 (d, 1 H), 7.73-7.68 (m, 2 H), 7.65 (d, 1 H), 7.55 (t, 1 H), 7.20-7.18 (m, 2 H), 7.09 (t, 1 H), 6.97 (d, 1 H), 4.76 (s, 2 H), 2.27 (s, 3 H).

Example 274:



672

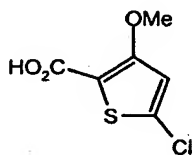
Step A:



673

(Reference: *Synthesis*, 1984, 847). Sulfury chloride (2 mL, 25.5 mmol) was added to a stirred mixture of methyl 3-methoxy-2-thiophenecarboxylate (Avocado, 4 g, 23.2 mmol) in CHCl_3 (40 mL). The reaction mixture was gently stirred for 4-6 h after which it was concentrated. The concentrate was dissolved in glacial AcOH and HCl gas was bubbled in. The resultant mixture was left standing for 48 h. Following solvent extraction and flash column chromatography on silica with CH_2Cl_2 , 673 (2.8 g, 58%) was obtained as a white solid. ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 3.7 (s, 3H), 3.9 (s, 3H), 7.3 (s, 1H).

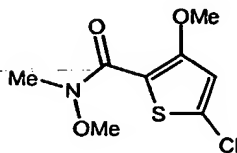
Step B:



674

673 (1 g, 4.8 mmol), lithium hydroxide dihydrate (1 g), EtOH (10 mL), and water (10 mL) were used according to general procedure III. Following work-up, 674 (0.59 g, 64%) was obtained as a light brown solid. ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 3.9 (s, 3H), 7.2 (s, 1H), 12.6 (br s, 1H).

Step C:

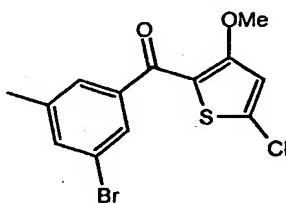


675

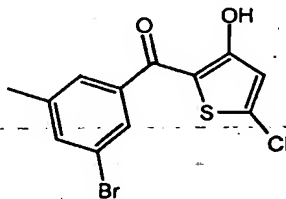
To a solution of 674 (0.59 g, 3.1 mmol) in THF (10 mL) was added carbonyl diimidazole (0.5 g, 3.1 mmol), N,O-dimethylhydroxylamine hydrochloride (0.45 g, 4.65 mmol), and a catalytic amount of N,N-dimethylaminopyridine. The reaction mixture was stirred at room temperature under argon for 24 h. The mixture was then diluted with EtOAc, and this was washed with water. After drying (MgSO_4) and solvent removal, the crude product was purified by flash column chromatography on silica gel with 5% MeOH in

390

CH₂Cl₂ to give **675** (0.36 g, 49%) as an off-white solid. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.1 (s, 3H), 3.7 (s, 3H), 3.9 (s, 3H), 7.2 (s, 1H).

Step D:**676**

675 (0.36 g, 1.5 mmol), 3,5-dibromotoluene (Avocado, 0.34 g, 1.4 mmol), and *n*-butyllithium (1.1 mL, 1.5 mmol of 1.4 M hexane solution) in ether were used according to general procedure VIII. Following work-up and flash column chromatography on silica with CH₂Cl₂, **676** (0.3 g, 58%) was obtained as a white solid. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.3 (s, 3H), 3.8 (s, 3H), 7.4 (s, 1H), 7.5 (s, 1H), 7.6 (s, 1H), 7.62 (s, 1H).

Step E:**677**

676 (0.3 g, 0.9 mmol), boron tribromide (1.7 mL, 1.7 mmol), and CH₂Cl₂ (10 mL) were used according to general procedure IX. **677** (0.26 g, 87%) was obtained as a solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.3 (s, 3H), 6.8 (s, 1H), 7.46 (s, 1H), 7.6 (s, 1H), 7.62 (s, 1H), 11.6 (s, 1H).

Step F:

A mixture of **677** (0.26 g, 0.8 mmol), **470** (0.24 g, 0.8 mmol) and potassium carbonate (0.6 g, 4 mmol) in DMF (10 mL) was stirred for 12 h. Water was added to the reaction mixture, which was in turn extracted with EtOAc. The EtOAc extract was further washed with water, brine and dried (MgSO₄). After solvent removal, the crude product was

subjected to flash column chromatography on silica gel with 5% MeOH in CH₂Cl₂ to give an impure 672, which was recrystallized from EtOAc. 672 (0.016 g, 4%) was obtained as a white solid. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.2 (s, 3H), 2.3 (s, 3H), 4.9 (s, 2H), 7.2 (s, 1H), 7.4 (s, 1H), 7.5-7.8 (m, 7H), 9.4 (s, 1H).

Example 275

Inhibition of Viral Replication

I. HeLa Cell Assay

The HeLa cell assay was performed according to a modification of Kimpton J. and Emerman M., Detection of replication-competent and pseudotyped human immunodeficiency virus with a sensitive cell line on the basis of activation of an integrated β-galactosidase gene, *J. Virol.* 66:2232-2239 (1992), in which HIV-1 infection is detected by the activation of an HIV-LTR driven β-galactosidase reporter that is integrated into the genome of a CD4⁺ HeLa cell line. Quantitation of β-galactosidase is achieved by measuring the activation of a chemiluminescent substrate (Tropix). The concentration of each compound required to inhibit 50% (IC₅₀) of the HIV-1 induced β-galactosidase signal, relative to untreated controls, was determined for each isogenic, recombinant virus.

A. Experimental Procedure

Growth and Maintenance of the CD4-HIV LTR-β-gal HeLa cell line.

HeLa-CD4-LTR-β-gal cells were obtained from the NIH AIDS Research and Reference Reagent Program. Cells were propagated in DMEM containing 10% fetal bovine serum, 0.2 mg/ml geneticin and 0.1 mg/ml hygromycin B. Cells were routinely split by trypsinization when confluency reached 80% (approximately every 2 to 3 days).

B. Construction of HIV-1 reverse transcriptase (RT) mutants

DNA encoding the HIV-1 reverse transcriptase was subcloned from a M13 phage into a general shuttle vector, pBCSK+, as a ~1.65 kbp EcoRI/HindIII ended DNA fragment. The HIV DNA insert of the resulting plasmid, pRT2, was completely sequenced on both strands prior to use in site directed mutagenesis experiments. Specific amino acid

replacements were made using Stratagene Quick Change reagents and mutagenic oligonucleotides from Oligos. Following mutagenesis, the entire mutant RT coding sequence was verified by sequencing both DNA strands.

5 C. Construction of isogenic HIV-1 RT mutant virus

Mutant HIV-1 strains were isolated by a modified Recombinant Virus Assay (Kellam P. and Larder B., Recombinant virus assay: a rapid, phenotypic assay for assessment of drug susceptibility of human immunodeficiency virus type 1 isolates, *Antimicrobial Agents and Chemotherapy*, 38:23-30, 1994). 1×10^7 Jurkat T-cells (maintained in RPMI containing 10% fetal bovine serum, split 1:5 every 5 to 6 days) were co-transfected with EcoRI/HindIII digested mutant RT plasmid and Bst EII-digested HIV-1_{HXB2ΔRT} DNA in the presence of DMRIE-C transfection reagent (Gibco) according to supplier's recommended protocol. Each mutant RT coding sequence was crossed into the RT-deleted HIV-1 viral DNA backbone by in vivo homologous recombination. Transfected cell
10 cultures were expanded and monitored until syncytia formation and CPE were extensive. Virus was harvested by clear spin of the culture supernatants and frozen at - 80 C as primary stock. Recombinant progeny virus was sequenced in the RT region to confirm the mutant genotype. Virus stocks were further expanded by infection of Jurkat cells, harvested and stored as frozen aliquots. Stocks were titered in HeLa MAGI cells for
15 assay.

20 D. Titering of virus stocks

The HIV-1_{HXB2} mutants were titered in the HeLa MAGI assay system to determine the relative light units (RLU) per ml, a measure of infectivity relevant for this assay system.
25 Virus stocks were diluted in a 2-fold series into DMEM containing 10% fetal bovine serum plus 20ug/ml DEAE-dextran and assayed as described in the Experimental Protocol section, below.

30 E. Experimental Protocol

96-well microtiter plate(s) (Costar #3598) were seeded with 3×10^3 HeLa-CD4-LTR-β-gal in 100μl DMEM containing 10% fetal bovine serum. Plates were placed in a 37 °C, 5% CO₂ humidified incubator overnight. The following day, mutant virus stocks were

thawed in a room temperature water bath and diluted into DMEM containing 10% fetal bovine serum and 20µg/ml DEAE-dextran to achieve an input of 1500 to 2000 RLU/ml. All media was removed with an 8 channel manifold aspirator and 35µl (50 to 70 total RLUs) of diluted virus was added to each well for virus adsorption. Plates were placed in a 37 °C, 5% CO₂ humidified incubator for 1.5 to 2 hours.

Compound titration plates were prepared at 1.35X final concentration during the virus adsorption period. Compounds were titrated robotically in a five-fold stepwise manner from 2.7 µM (2µM final) to 1.35 pM (1pM final). This scheme allows 8 compounds to be tested per 96-well plate with 10 dilution points and 2 controls per compound (n=1). Compounds were titrated into DMEM containing 10% fetal bovine serum plus 0.135% DMSO (0.1% final). 100µl of titrated compound was removed from every well of the titration plate and added to the virus adsorption plate. Plates were placed in a 37 °C, 5% CO₂ humidified incubator for 72 hours.

Following incubation, supernatants were aspirated from every well as described above and 100µl of phosphate buffered saline was added. The PBS was then aspirated as above and 15µl of lysis buffer (Tropix) was added. Plates were maintained at room temperature for 10 minutes during which time the chemiluminescent substrate (Tropix) was diluted 1:50 into room temperature substrate dilution buffer (Tropix). 100µl of diluted substrate was then added to each well. Plates were incubated at room temperature for 1 to 1.5 hours. Following incubation, the chemiluminescence of each well was measured with a Dynatech plate reader using the following settings:

PARAMETER	VALUE
run	cycle
data	all
gain	low
cycles	1s
pause	2s
rows	abcdefgh
temp	room
stir	off

The output raw data, RLUs, were analyzed by nonlinear regression to determine IC₅₀ values (see data analysis section below).

F. Data Analysis

Relative light units (RLU) are expressed as % control:

5
$$(\text{RLU at compound []} / \text{RLU no compound}) * 100 = \% \text{ Control}$$

The concentration of compound that inhibits 50% of the signal produced in untreated samples (IC_{50}) is determined by the following nonlinear regression model available on the ROBOSAGE software package:

10

$$Y = V_{\max} * (1 - (X^n / (K^n + X^n)))$$

This equation describes a sigmoidal inhibition curve with a zero baseline. X is inhibitor concentration and Y is the response being inhibited. V_{\max} is the limiting response as X approaches zero. As X increases without bound, Y tends toward its lower limit, zero. K is the IC_{50} for the inhibition curve, that is, Y is equal to 50% of V_{\max} when $X = K$.

15

Results in Table 1 are reported as ranges of representative IC_{50} values.

20 II. MT4 Cell Assay

A. Experimental Procedure

Antiviral HIV activity and compound-induced cytotoxicity were measured in parallel
25 by means of a propidium iodide based procedure in the human T-cell lymphotropic virus transformed cell line MT4. Aliquots of the test compounds were serially diluted in medium (RPMI 1640, 10% fetal calf serum (FCS), and gentamycin) in 96-well plates (Costar 3598) using a Cetus Pro/Pette. Exponentially growing MT4 cells were harvested and centrifuged at 1000 rpm for 10 min in a Jouan centrifuge (model CR 4 12). Cell
30 pellets were resuspended in fresh medium (RPMI 1640, 20% FCS, 20% IL-2, and gentamycin) to a density of 5×10^5 cells/ml. Cell aliquots were infected by the addition of HIV-1 (strain IIIB) diluted to give a viral multiplicity of infection of 100 x TCID₅₀. A similar cell aliquot was diluted with medium to provide a mock-infected control. Cell infection was allowed to proceed for 1 hr at 37°C in a tissue culture incubator with
35 humidified 5% CO₂ atmosphere. After the 1 hr incubation the virus/cell suspensions were diluted 6-fold with fresh medium, and 125 µl of the cell suspension was added to each

well of the plate containing pre-diluted compound. Plates were then placed in a tissue culture incubator with humidified 5% CO₂ for 5 days. At the end of the incubation period, 27 µl of 5% Nonidet-40 was added to each well of the incubation plate. After thorough mixing with a Costar multtip pipetter, 60 µl of the mixture was transferred to filter-bottomed 96-well plates. The plates were analyzed in an automated assay instrument (Screen Machine, Idexx Laboratories). The control and standard used was 3'-azido-3'-deoxythymidine tested over a concentration range of 0.01 to 1 µM in every assay. The expected range of IC₅₀ values for 3'-azido-3'-deoxythymidine is 0.04 to 0.12 µM. The assay makes use of a propidium iodide dye to estimate the DNA content of each well.

B. Analysis

The antiviral effect of a test compound is reported as an IC₅₀, i.e. the inhibitory concentration that would produce a 50% decrease in the HIV-induced cytopathic effect. This effect is measured by the amount of test compound required to restore 50% of the cell growth of HIV-infected MT4 cells, compared to uninfected MT4 cell controls. IC₅₀ was calculated by RoboSage, Automated Curve Fitting Program, version 5.00, 10-Jul-1995.

For each assay plate, the results (relative fluorescence units, rfU) of wells containing uninfected cells or infected cells with no compound were averaged, respectively. For measurements of compound-induced cytotoxicity, results from wells containing various compound concentrations and uninfected cells were compared to the average of uninfected cells without compound treatment. Percent of cells remaining is determined by the following formula:

Percent of cells remaining = (compound-treated uninfected cells, rfU / untreated uninfected cells) x 100.

A level of percent of cells remaining of 79% or less indicates a significant level of direct compound-induced cytotoxicity for the compound at that concentration. When this condition occurs the results from the compound-treated infected wells at this concentration are not included in the calculation of IC₅₀.

For measurements of compound antiviral activity, results from wells containing various compound concentrations and infected cells are compared to the average of uninfected and infected cells without compound treatment. Percent inhibition of virus is determined by the following formula:

Percent inhibition of virus = $(1 - ((\text{ave. untreated uninfected cells} - \text{treated infected cells}) / (\text{ave. untreated uninfected cells} - \text{ave. untreated infected cells}))) \times 100$

References:

1. Averett, D.R., Anti-HIV compound assessment by two novel high capacity assays, *J. Virol. Methods* 23: 263-276, 1989.
2. Schwartz, O., et al., A rapid and simple colorimetric test for the study of anti-HIV agents, *AIDS Res. and Human Retroviruses* 4 (6): 441-447, 1988..
3. Daluge, S.M., et al., 5-chloro-2'3'-deoxy-3'fluorouridine (935U83), a selective anti-human immunodeficiency virus agent with an improved metabolic and toxicological profile. *Antimicro. Agents and Chemother.* 38 (7): 1590-1603, 1994..
4. Dornsife, R.E., et al., Anti-human immunodeficiency virus synergism by zidovudine (3'-azidothymidine) and didanosine (dideoxyinosine) contrasts with the additive inhibition of normal human marrow progenitor cells, *Antimicro. Agents and Chemother.* 35 (2): 322-328, 1991.

Results in Table 1. are expressed as representative IC₅₀ ranges.

Table 1

Compound Number	Virus Type	IC ₅₀ (nM) Range *	Assay
1	HIV-1	C	MT4
	NEV-R	D	MT4
5	HIV-1	B	MT4
	NEV-R	C	MT4
8	HIV-1	B	MT4
	NEV-R	C	MT4
9	HIV-1	B	MT4
	NEV-R	C	MT4
62	HIV-1	A	MT4
	HIV-2	D	MT4
	NEV-R	A	MT4
	E138K	A	HeLa
	G190A	A	HeLa
	G190E	A	HeLa
	K101E	A	HeLa
	K103N	A	HeLa
	K103N/G190A	B	HeLa
	K103N/L1001	A	HeLa

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		K103N/P225H	A	HeLa
		K103N/V1081	A	HeLa
		K103N/Y181C	B	HeLa
		L1001	A	HeLa
5		P225H	A	HeLa
		P236L	B	HeLa
		V106A	B	HeLa
		V106A/Y181C	B	HeLa
		V1061	A	HeLa
10		V1061/Y181C	B	HeLa
		V1081	A	HeLa
		V1081/Y181C	A	HeLa
		WTRVA	A	HeLa
		Y181C	A	HeLa
15		Y188C	A	HeLa
	78	HIV-1	A	
		NEV-R	A	
		E138K	A	HeLa
20		G190A	A	HeLa
		G190E	A	HeLa
		K101E	A	HeLa
		K103N	A	HeLa
		K103N/G190A	B	HeLa
25		K103N/L1001	A	HeLa
		K103N/P225H	A	HeLa
		K103N/V1081	A	HeLa
		K103N/Y181C	A	HeLa
		L1001	A	HeLa
30		P225H	A	HeLa
		P236L	A	HeLa
		V106A	B	HeLa
		V106A/Y181C	B	HeLa
		V1081	A	HeLa
35		V1081/Y181C	B	HeLa
		WTRVA	A	HeLa
		Y181C	A	HeLa
		Y188C	A	HeLa
40	79	HIV-1	A	MT4
		HIV-2	D	MT4
		NEV-R	A	MT4
		K103N	A	HeLa
		K103N/Y181C	A	HeLa
45				
	103	HIV-1	B	MT4
		NEV-R	C	MT4
		K103N	B	HeLa
50				
	120	HIV-1	B	MT4
		NEV-R	B	MT4
		K103N	B	HeLa
		K103N/Y181C	C	HeLa
55		WTRVA	B	HeLa
		Y181C	B	HeLa

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	122	HIV-1	A	MT4
		NEV-R	B	MT4
		K103N	B	HeLa
5		K103N/Y181C	D	HeLa
		WTRVA	B	HeLa
		Y181C	C	HeLa
10				
	239	HIV-1	A	MT4
		NEV-R	A	MT4
		E138K	A	HeLa
		G190A	A	HeLa
15		G190E	A	HeLa
		K101E	A	HeLa
		K103N	A	HeLa
		K103N/G190A	B	HeLa
		K103N/L1001	A	HeLa
20		K103N/P225H	A	HeLa
		K103N/V1081	A	HeLa
		K103N/Y181C	B	HeLa
		L1001	A	HeLa
25		P225H	A	HeLa
		P236L	A	HeLa
		V106A	B	HeLa
		V106A/Y181C	C	HeLa
		V1061	A	HeLa
30		V1061/Y181C	A	HeLa
		V1081	A	HeLa
		V1081/Y181C	A	HeLa
		WTRVA	A	HeLa
		Y181C	A	HeLa
35		Y188C	A	HeLa
	257	HIV-1	A	MT4
		NEV-R	A	MT4
		E138K	A	HeLa
40		G190A	A	HeLa
		G190E	A	HeLa
		K101E	A	HeLa
		K103N	A	HeLa
		K103N/G190A	B	HeLa
45		K103N/L1001	A	HeLa
		K103N/P225H	A	HeLa
		K103N/V1081	A	HeLa
		K103N/Y181C	A	HeLa
		L1001	A	HeLa
50		P225H	A	HeLa
		P236L	A	HeLa
		V106A	B	HeLa
		V106A/Y181C	B	HeLa
		V1061	A	HeLa
55		V1061/Y181C	B	HeLa
		V1081	A	HeLa
		V1081/Y181C	A	HeLa

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		WTRVA	A	HeLa
		Y181C	A	HeLa
		Y188C	A	HeLa
5				
	338	HIV-1	A	MT4
		NEV-R	B	MT4
		K103N	B	HeLa
		K103N/Y181C	C	HeLa
10		WTRVA	A	HeLa
		Y181C	B	HeLa
	387	HIV-1	A	MT4
		NEV-R	B	MT4
15		K103N	A	HeLa
		K103N/Y181C	B	HeLa
		WTRVA	A	HeLa
		Y181C	B	HeLa
20	435	HIV-1	A	MT4
		NEV-R	B	MT4
		K103N	A	HeLa
		K103N/Y181C	C	HeLa
25		WTRVA	A	HeLa
		Y181C	B	HeLa
	448	HIV-1	A	MT4
		HIV-2	D	MT4
		NEV-R	A	MT4
30		E138K	A	HeLa
		G190A	A	HeLa
		G190E	A	HeLa
		K101E	A	HeLa
		K103N	A	HeLa
35		K103N/G190A	B	HeLa
		K103N/L1001	A	HeLa
		K103N/P225H	A	HeLa
		K103N/V1081	A	HeLa
		K103N/Y181C	B	HeLa
40		L1001	A	HeLa
		P225H	A	HeLa
		P236L	B	HeLa
		V106A	B	HeLa
		V106A/Y181C	B	HeLa
45		V1061	A	HeLa
		V1061/Y181C	B	HeLa
		V1081	A	HeLa
		V1081/Y181C	A	HeLa
		Y181C	A	HeLa
50		Y188C	A	HeLa
	453	HIV-1	A	MT4
		NEV-R	A	MT4
		G190A	A	HeLa
55		K101E	A	HeLa
		K103N	A	HeLa
		K103N/G190A	B	HeLa

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		K103N/P225H	A	HeLa
		K103N/V1081	A	HeLa
		K103N/Y181C	A	HeLa
		L1001	A	HeLa
5		P225H	A	HeLa
		P236L	B	HeLa
		V106A	C	HeLa
		V106A/Y181C	B	HeLa
		V1061	A	HeLa
10		V1061/Y181C	B	HeLa
		V1081	C	HeLa
		V1081/Y181C	A	HeLa
		WTRVA	A	HeLa
		Y181C	A	HeLa
15		Y188C	A	HeLa
	491	HIV-1	A	MT4
		NEV-R	A	MT4
		G190A	A	HeLa
20		K103N	A	HeLa
		K103N/G190A	B	HeLa
		K103N/P225H	A	HeLa
		K103N/V1081	A	HeLa
		K103N/Y181C	A	HeLa
25		L1001	A	HeLa
		P225H	A	HeLa
		P236L	A	HeLa
		V106A/Y181C	A	HeLa
		V1061	A	HeLa
30		V1061/Y181C	B	HeLa
		V1081	A	HeLa
		V1081/Y181C	A	HeLa
		WTRVA	A	HeLa
		Y181C	A	HeLa
35				
	564	HIV-1	A	MT4
		NEV-R	A	MT4
		G190A	A	HeLa
40		K103N	A	HeLa
		K103N/G190A	A	HeLa
		K103N/P225H	A	HeLa
		K103N/V1081	A	HeLa
		K103N/Y181C	A	HeLa
45		L1001	A	HeLa
		P225H	A	HeLa
		P236L	A	HeLa
		V106A/Y181C	A	HeLa
		V1061	A	HeLa
50		V1061/Y181C	A	HeLa
		V1081/Y181C	A	HeLa
		WTRVA	A	HeLa
		Y181C	A	HeLa
55	587	HIV-1	A	MT4
		NEV-R	A	MT4
		G190A	A	HeLa

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		K103N	A	HeLa
		K103N/G190A	A	HeLa
		K103N/P225H	A	HeLa
5		K103N/V108I	A	HeLa
		K103N/Y181C	A	HeLa
		L100I	A	HeLa
		P225H	A	HeLa
		P236L	A	HeLa
10		V106A/Y181C	A	HeLa
		V106I	A	HeLa
		V106I/Y181C	B	HeLa
		V108I	A	HeLa
		V108I/Y181C	A	HeLa
15		WTRVA	A	HeLa
		Y181C	A	HeLa
	475	HIV-1	A	MT4
		NEV-R	A	MT4
20		G190A	A	HeLa
		K103N	A	HeLa
		K103N/G190A	A	HeLa
		K103N/P225H	A	HeLa
		K103N/V108I	A	HeLa
25		K103N/Y181C	A	HeLa
		L100I	A	HeLa
		P225H	A	HeLa
		P236L	A	HeLa
		V106A/Y181C	A	HeLa
30		V106I	A	HeLa
		V106I/Y181C	B	HeLa
		V108I	A	HeLa
		V108I/Y181C	A	HeLa
		WTRVA	A	HeLa
35		Y181C	A	HeLa
	478	HIV-1	A	MT4
		NEV-R	A	MT4
40		G190A	A	HeLa
		K103N	A	HeLa
		K103N/G190A	A	HeLa
		K103N/P225H	A	HeLa
		K103N/V108I	A	HeLa
45		K103N/Y181C	A	HeLa
		L100I	A	HeLa
		P225H	A	HeLa
		P236L	A	HeLa
		V106A/Y181C	A	HeLa
50		V106I	A	HeLa
		V106I/Y181C	A	HeLa
		V108I	A	HeLa
		V108I/Y181C	A	HeLa
		WTRVA	A	HeLa
55		Y181C	A	HeLa
	498	HIV-1	A	MT4
		NEV-R	A	MT4

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		G190A	A	HeLa
		K103N	A	HeLa
		K103N/G190A	A	HeLa
		K103N/P225H	A	HeLa
5		K103N/V1081	A	HeLa
		K103N/Y181C	A	HeLa
		L100I	A	HeLa
		P225H	A	HeLa
		P236L	A	HeLa
10		V106A/Y181C	A	HeLa
		V106I	A	HeLa
		V106I/Y181C	B	HeLa
		V108I	A	HeLa
		V108I/Y181C	A	HeLa
15		WTRVA	A	HeLa
		Y181C	A	HeLa
	593	HIV-1	A	MT4
20		NEV-R	A	MT4
		G190A	A	HeLa
		K103N	A	HeLa
		K103N/G190A	A	HeLa
		K103N/P225H	A	HeLa
25		K103N/V1081	A	HeLa
		K103N/Y181C	A	HeLa
		L100I	A	HeLa
		P225H	A	HeLa
		P236L	A	HeLa
30		V106A/Y181C	A	HeLa
		V106I	A	HeLa
		V106I/Y181C	B	HeLa
		V108I	A	HeLa
		V108I/Y181C	A	HeLa
35		WTRVA	A	HeLa
		Y181C	A	HeLa
	483	HIV-1	B	MT4
40		NEV-R	A	MT4
		K103N	C	HeLa
		V106A/Y181C	C	HeLa
		V106I	A	HeLa
		V106I/Y181C	B	HeLa
45		WTRVA	B	HeLa
		Y181C	C	HeLa
	637	HIV-1	A	MT4
		NEV-R	A	MT4
50		G190A	A	HeLa
		K103N	A	HeLa
		K103N/G190A	A	HeLa
		K103N/P225H	A	HeLa
		K103N/V1081	A	HeLa
55		K103N/Y181C	A	HeLa
		L100I	A	HeLa
		P225H	A	HeLa

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		P236L	A	HeLa
		V106A/Y181C	A	HeLa
		V106I	A	HeLa
		V106I/Y181C	A	HeLa
5		V108I/Y181C	A	HeLa
		WTRVA	A	HeLa
		Y181C	A	HeLa
	503	HIV-1	A	MT4
10		NEV-R	A	MT4
		G190A	A	HeLa
		K103N	A	HeLa
		K103N/G190A	A	HeLa
		K103N/P225H	A	HeLa
15		K103N/V108I	A	HeLa
		K103N/Y181C	A	HeLa
		L100I	A	HeLa
		P225H	A	HeLa
		P236L	A	HeLa
20		V106A/Y181C	A	HeLa
		V106I	A	HeLa
		V106I/Y181C	A	HeLa
		V108I	A	HeLa
		V108I/Y181C	A	HeLa
25		WTRVA	A	HeLa
		Y181C	A	HeLa
	601	HIV-1	A	MT4
30		NEV-R	A	MT4
		K103N	A	HeLa
		WTRVA	A	HeLa
		Y181C	A	HeLa
		V106A	A	HeLa

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- * A indicates an IC_{50} of 10nM or less
 B indicates an IC_{50} between 11nM and 100nM
 C indicates an IC_{50} between 101nM and 1,000nM
 D indicates an IC_{50} between 1,000nM and 3,000nM